

BULLETIN
OF
THE JOHNS HOPKINS HOSPITAL

(THE PUBLICATION OF THE MEDICAL SCHOOL AND HOSPITAL)

(SUPPORTED BY THE DE LAMAR FUND OF THE JOHNS HOPKINS UNIVERSITY)

EDITORIAL BOARD

Managing Editor, HENRY N. HARKINS

Associate Managing Editor, JOHN A. LUETSCHER, JR.

E. COWLES ANDRUS

CHARLES R. AUSTRIAN

W. HALSEY BARKER

JAMES BORDLEY, III

JOHN EAGER HOWARD

ARNOLD R. RICH

VOLUME LXXX

BALTIMORE
THE JOHNS HOPKINS PRESS
1947

COPYRIGHT, 1947
BY THE JOHNS HOPKINS PRESS

OBJECTIVE STUDIES OF SOME PHYSIOLOGIC RESPONSES IN MILD CHRONIC TRENCH FOOT*

G. E. BURCH, M.D.,¹ MAJOR HARVEY L. MYERS, M.C.,¹ LT. COL. RENO
R. PORTER, M.C.,² AND MAJOR NATHAN SCHAFER, M.C.¹

TABLE OF CONTENTS

- I. Introductory Remarks
 - 1. Object of study
 - 2. Rationale of study
- II. Methods and Materials
 - 1. Procedure of study in general
 - 2. The subjects
 - a. Where from
 - b. Where injured
 - c. Enumeration and brief description of
 - d. Clinical evaluation of trench foot
 - (1) Class I—subgroups a, b, c
 - (2) Class II
 - (3) Class III
 - e. Control subjects
 - 3. Conditions in the observation room and preparation of subjects
 - a. Conditions of temperature, humidity and air currents prevailing in control room
 - b. Clothing worn during test and its influence on results
 - c. Weather conditions in New Orleans and their possible influence upon subjects in control room
 - d. Preliminary preparation of patients before entering control room
 - (1) Eating
 - (2) Smoking
 - (3) Drinking
 - (4) Coexisting disease
 - 4. Description of the occlusion-reactive hyperemia test
- III. The Experiments
 - A. Occlusion-reactive Hyperemia Test
 - 1. Normal subjects and patients with trench foot
 - 2. Psychoneurotic subjects and patients with trench foot
 - 3. Posterior tibial nerve block
 - (a) Trench foot only
 - (b) Normal males

* Aided by a contract with the O. S. R. D. (Contract Number M-5592), the Rockefeller Foundation and the Helis Institute for Medical Research.

¹ From the Department of Medicine, Tulane Medical School, New Orleans.

² From the Medical Department of the U. S. Army.

Col. A. P. Upthur, M. C., Commanding Officer of the LaGarde General Hospital provided significant assistance in these studies.

- (c) Psychoneurotic
- (d) Normal females
- 4. Patients with miscellaneous peripheral vascular diseases
- B. Miscellaneous Quasi-objective Tests
 - 1. State of "Vascular Tone" (Naide)
 - 2. Skin color
 - 3. Reactive hyperemia
 - 4. Rate of refilling of pressure emptied skin vessels
- C. Temperature of Various Parts of Foot at Rest
- D. Rate of Water Loss Through Skin and Sweating
- IV. General Discussion
 - A. Tests for the Evaluation of Mild Chronic Trench Foot:
Enumeration of Tests and Testing Conditions
 - 1. Room conditions
 - 2. Preparation of subject
 - 3. Fifteen minute temperatures of parts
 - 4. Rate of refilling of pressure emptied skin vessels
 - 5. Occlusion-reactive hyperemia test
 - B. Interpretation of Tests
 - 1. Interpretation of 15 minute temperature determinations
 - 2. Interpretation of rate of refilling of pressure emptied skin vessels
 - 3. Interpretation of occlusion-reactive hyperemia test
 - 4. Interpretation of combination of 1, 2, and 3 above
- V. Summary and Conclusions

I. INTRODUCTORY REMARKS

The clinical picture of trench foot has been exhaustively described in the literature by many authors. It is not the purpose of this report to review the problem of trench foot. A well accepted symptom complex as well as clinical observations have been delineated in all of its phases from its inception until the late chronic phase of the disease. This work is to be limited to a series of physiologic observations on mild chronic trench foot of a degree bordering on normalcy which might ultimately lead to the improvisation of a simple objective test which can not only demonstrate the existence of trench foot but also, to some extent, the degree of severity, or at least differentiate between the presence or absence of activity. An absolutely infallible test is certainly not available, but the results strongly suggest that it is possible to demonstrate the existence of activity and degree of involvement. It is well to realize that data obtained on chronic trench foot with mild involvement will differ qualitatively and quantitatively from those of the acute phases of the disease. There is a high negative

correlation between the time at which the injury was incurred and the acuteness of the process at the time of testing. The tests to be described tend to indicate that the trench foot process is in reality an inflammatory process, an inflammatory process produced as a result of injury from physical agents, namely cold and wet. This injury, aggravated by constricting foot gear, prolonged dependency, immobilization, deficient nutrition and so on, may be superimposed with secondary infections entering through avenues provided by tissue destruction. Trichophytosis, which is very common among patients with trench foot, may also provide avenues of entrance for secondary infections. Inflammation, as defined by Dorland, (1), is "the condition into which tissues enter as a reaction to injury (Adami). Inflammation is characterized by pain, heat, redness and swelling, histologically by hyperemia, stasis, changes in the blood and walls of the small vessels and by various exudations." Inflammation falls into acute, subacute, and chronic stages. The acute inflammation, as far as trench foot is concerned, is first manifested by intense hyperemia. There is swelling, redness and pain in a warm extremity. This acute phase has been referred to as the *hyperemic or inflammatory stage*. It may last from a few days to a few weeks. Subacute and chronic stages of inflammation may be designated as the *posthyperemic* (apparently a misnomer) stage, during which time reaction is subsiding and repair has begun. The transition from the stage of acute inflammatory reaction to the stage of repair is insidious and extremely variable. These two stages always overlap, so that while a limited amount of the early type of reaction still exists, repair may be in full swing.

Although the literature on the pathology of trench foot leaves many questions unanswered, both gross and microscopic studies repeatedly refer to tissue changes which leave no doubt of their identity with inflammation, involving not only the epidermis and its appendages, such as the sweat glands, hair follicles and sebaceous glands, but also the dermis, subcutaneous tissues, fat, muscle, nerve, bone and, of course, the blood vessels. These evidences of inflammation were found not only in acute stages but also many months after the initial injury (2).

Since the manifestations of inflammation are pain, redness, swelling

and heat, observations of these cardinal features will indicate the presence and degree of inflammation. Pain is very difficult to evaluate objectively. Variations in the amount of circulating hemoglobin, pigmentation, thickness of the epidermis, and lighting, limit skin color studies as a means of evaluating circulation. Swelling, especially in the late or chronic phases of disease, may exist and frequently does, but its measurement is a practical problem difficult to surmount. Temperature, on the other hand, may be easily and accurately measured (0.1 to $0.2^{\circ}\text{C}.$) by means of thermocouples. Because of this, the study has been mainly limited to the use of thermocouples. It is purely an objective method which is not subject to influences. The temperature of a part is closely correlated with the degree of inflammation in that part, providing other factors which produce elevated temperature can be ruled out. These factors are usually constitutional rather than local. For example, if the individual is experiencing an elevation of temperature due to generalized disease, this will, of course, be reflected in the extremities. An endocrine imbalance, such as hyperthyroidism, will cause the extremities to become warm. Psychogenic factors will influence the temperature of an extremity. In the course of these studies an attempt was made to eliminate the extraneous local and general causes for elevation of the temperature of a part and evaluate only the temperature changes produced by factors intrinsic in the part which bears relationship to the trench foot.

Assuming that the temperature of the part will be an index of the existence and degree of inflammation in that part both as to reaction and repair a person with severe trench foot may have a lower surface temperature of the part involved than one with a mild case, if these two determinations are made at different times in relation to the time of onset. For example, the patient may have a considerable degree of tissue damage and tissue loss with only moderate deviation of the temperature above normal, providing the relationship between the date of onset of the trench foot and the determination of the temperature are sufficiently far apart. When tissue loss or severe damage is present it is usually obvious to the examiner. A test which could demonstrate the existence of inflammation in the presence of a minimum amount of clinical evidence of damage would be of great value. In brief, at the conclusion of the various physiologic studies described

below a significant problem may be summarized as to confirm or to deny the existence of inflammation in mild chronic trench foot in the absence of definite objective findings, and in spite of subjective complaints.

The exact pathogenesis of trench foot is not known. It has not been definitely established that all injuries resulting from cold or low temperature may be placed in one category from the standpoint of tissue pathology. Certainly, tissue injuries produced by chilling under conditions much below freezing may differ from injuries produced by temperatures above freezing. "Wet Cold" is especially damaging because water has a high capacity for removing heat by conduction from an extremity, about 27 times that of air. Therefore, exposure under weather conditions existing during a thaw may result in greater disability than is incurred in actual freezing temperature because of the influence of the water. Exposure to "wet cold" for prolonged periods, of course, will produce a more profound and far reaching reduction of tissue temperature of the exposed part than short exposures. "True frostbite" does not show uniform necrosis throughout the deeper tissues, although areas of pathology similar to those found in tissues subjected to temperatures above freezing may be seen. All other factors being equal, "wet cold" produces a more diffuse or penetrating effect than "dry cold" just as "wet heat" produces a more diffuse and penetrating effect than "dry heat". This may account for the fact that although trench foot may demonstrate less superficial involvement of tissue, the disability in trench foot patients may be greatly prolonged over patients with frostbite in which the degree of superficial tissue destruction is much greater. The diffuse and deep injury to tissues tends to explain the existence of an inflammatory process months and possibly even years after the initiating cause has been removed. The premise that inflammation, including both reaction as well as repair, may reside in tissues long after the initial injury is by no means a new one, peculiar to trench foot. Burns, particularly scalds, which may be associated with little evidence of superficial reaction in the later stages, may result in prolonged disability due to diffuse deep tissue damage. Certainly, burns produced by chemicals and radiation result in chronic reaction in tissues. Inflammation under these circumstances may exist long after the initiating cause has been removed (3, 4).

II. METHODS AND MATERIALS

1. *Procedure of Study in General*

The subjects were made to rest in bed, unclothed and covered with a sheet in an air conditioned room. Thermocouples were placed upon the upper and lower extremities. After stabilization of skin temperatures was obtained, the arterial and venous circulations to the legs were suddenly occluded bilaterally by a pressure cuff around the lower third of the thigh. After 15 minutes of occlusion the pressure was released and circulation re-established. Temperature determinations were made continuously *ad seriatum* throughout the period of study. During the course of these observations, variations in skin color, intensity and duration of reactive hyperemia, and rate of refilling of skin vessels were noted. The additional procedure of unilateral blocking of the posterior tibial nerve with procaine was performed in some of the studies. Identical observations were made on both trench foot and control subjects, simultaneous studies being conducted whenever practicable.

A group of subjects, both normal and those with trench foot, were observed for insensible and sensible perspiration. Sensible perspiration was initiated by a very hot and humid environment.

2. *The Subjects*

The subjects studied were:

Trench Foot Patients: Patients with uncomplicated trench foot were transferred by railroad from the Brooke General Hospital of the U. S. Army and the U. S. Army General Hospital at Camp Butner, North Carolina, to the LaGarde General Hospital of the U. S. Army at New Orleans. They were then transported, via ambulances, from the LaGarde Hospital to the laboratories at Tulane Medical School for observation. With only a few exceptions the patients were ambulatory. The patients were mainly injured during the "Battle of the Bulge" in Belgium. The date of injury and length of time since injury are indicated in detail in Table 1. Also shown in Table 1 are details of age, duration of trench foot symptoms, degree of damage, and other miscellaneous factors of clinical and biographical interest. The patients with trench foot totaled 46, and ranged from 19 to 36 years in age. All of them were males; 44 white and two colored.

To correlate the laboratory findings with the clinical manifestations it became necessary to classify the patients under study into clinical types, or classes, of severity. Although it would have been valuable to include in this classification the severity of the initial state, it was impossible to evaluate this because of the meager information available on the medical record and the unreliability of the past medical history derived from each patient. Furthermore, since the present studies were concerned primarily with the chronic phases of the disease, this information was not essential. The classification employed in these patients was made simple and depended mainly on objective clinical data. The classification as used elsewhere (5) obviously could not be employed in these patients.

Classification of the Chronic Stage of Trench Foot: Class I: (a) Patients with practically no objective findings, all complaints being subjective in nature. Existence of disease may even be subject to question. (b) Patients with mild erythema of toes, slight dependent edema, and some slight limitation of motion of the toes. (c) Patients with obvious edema, definite erythema, tenderness on pressure, limitation of motion of toes, and possible small ulcerations or areas of desquamation, and with obvious walking difficulties.

Class II: Patients with swelling, erythema, definite loss of tissue, not including spontaneous amputation of an entire toe; some fairly large areas of ulceration and tissue loss. The patient is able to stand on his feet with some difficulty.

Class III: Patients with spontaneous amputation of at least one toe, marked reaction of inflammation with edema and erythema. Patient is unable to walk and has pain even while at rest in bed.

Since almost all of these patients were of *Class I* and they varied in degree within this Class, the Class was further subdivided into three subclasses. Therefore, with such a classification, it was possible to code the severity of the patients by symbols. For example, Ib would be employed to indicate a patient with chronic trench foot of Class I and subclass b, and so on.

Normal Subjects: There were 108 normal volunteer subjects varying in age from 19 to 40 years. There were 89 males and 19 females (latter volunteers from the Women's Army Corps). The males were soldiers from the detachment at LaGarde General Hospital, a few

TABLE 1

SUBJECT	AGE	HOME STATE	MONTHS IN SERVICE	WHERE SYMPTOMS BEGAN	DATE ONSET OF SYMPTOMS	DATE OFF LINE	TIME IN MTHS. FROM ONSET TO TIME STUDIED	PREVIOUS FOOT TROUBLE	PREVIOUS TROUBLE WITH TEMP. CHANGES	CLINICAL EVALUATION		AMPUTATIONS
										At onset	At present	
G.I.	25	Ill.	15	Belgium	1/ 8/45	1/10/45	5	None	None	Mod.	1c	None
J.S.	19	Ala.	14	Belgium	1/ 9/45	1/10/45	5	None	None	Severe	111	1, 2, and 3rd. toes rt. ft. all toes lt. ft.
E.A.W.	23	Tenn.	62	Belgium	12/28/44	1/ 7/45	5	None	None	Severe	111	All toes both feet.
D.E.I.	19	Mo.	14	Belgium	1/10/45	1/12/45	5	None	None	Severe	111	All toes both feet.
C.E.C.	22	Ala.	29	France	12/ 3/44	12/ 5/44	6	None	None	Mod.	1a	None
W.F.	19	Ark.	15	France	2/ 7/45	2/ 7/45	4	None	None	Mod.	1c	None
H.A.D.	22	Ohio	12	Belgium	12/28/44	1/23/45	4½	None	Cramp in feet while swimming	Mod.	1c	None
F.P.W.	26	Texas	68	Belgium	12/25/44	1/ 2/45	6	Flat feet	None	Severe	111	All toes right foot.
J.A.	23	Ala.	43	Germany	11/22/44	11/28/44	7½	Burnt as a child both ft.	Both legs fracture	Mod.	1c	None
S.J.C.	20	La.	23	France	1/ 2/45	1/ 6/45	5½	Flat feet	None	Mod.	1b	None
W.H.	24	Miss.	13	Germany	1/12/45	2/ 3/45	5	None	Swimming cramps legs thighs	Mod.	1c	None
L.B.J.	22	Wisc.	23	Belgium	12/19/44	12/23/44	5½	None	Frostbite feet.	Severe	111	First and second toe left foot.

Detail clinical and biographical information on the patients with chronic Trench Foot are included in these studies.

E.G.C. C.L.	25 24	Ill. Tenn.	12 36	Germany Belgium	1/11/45 1/21/45	1/24/45 1/21/45	4½ 7½	None None	None None	Severe Mod.	1b 111	None Fourth and fifth toe right foot.
L.P.C. B.A.S.	23 19	La. Texas	27 13	France Germany	3/15/45 2/24/45	3/15/45 2/24/45	7 6½	None None	None None	Mod. Mod.	1a 1a	None None
G.H.L. R.H.H.	22 22	Texas Texas	36 33	Germany France	2/ 2/45 12/ 9/44	2/ 2/45 12/ 9/44	7 9	None None	None None	Mod. Mod.	1a 1b	None None
H.J.G. E.W.H.	24 23	Ala. Ark.	11 30	Germany Belgium	1/10/45 1/ 5/45	1/10/45 1/ 5/45	6 8	None None	None None	Mod. Mod.	1a 1a	None None
J.W.G. W.T.	25 19	Wisc. Okla.	24 8	Germany France	2/ 9/45 2/ 5/45	2/ 9/45 2/ 7/45	7 4	None Flat ft.	None None	Mod. Severe	1a 111	None First and sec. ond toes right foot.
C.M.G.	23	Texas	13	Luxem.	1/15/45	1/28/45	4½	None	Cramp in foot while swim- ming	Mod	1a	None
E.C.Mc. H.L.J.	30 25	Ark. Ala.	12 13	France Belgium	11/15/44 1/ 8/45	11/18/44 1/ 8/45	7½ 6	None None	None None	Mod. Mod.	1a 1a	None None
L.H.L.	19	Ark.	11	Luxem.	1/21/45	1/21/45	4½	None	Cramp while swimming	Severe	1a	None
L.L.N. B.C.	34 25	N.C. Texas	16 33	Italy Italy	1/ 7/45 4/14/45	1/ 7/45 4/14/45	5 5	None None	None None	Severe Mod.	1b 1a	None None
R.L.T. S.W.N.	19 25	Mich. Pa.	12 14	Belgium Germany	1/11/45 2/ 5/45	1/11/45 2/ 5/45	5½ 7	None None	None None	Mod. Mod.	1a 1a	None None
W.O.S. J.L.D.	24 22	Texas Ala.	34 27	Germany Belgium	2/ 9/45 1/25/45	2/ 9/45 1/25/45	7 4	None None	None Cramp while swimming	Mod. Severe	1a 1b	None None
G.J. B.K.	33 34	Mich. Pa.	35 14	Germany Germany	1/28/45 12/14/44	1/28/45 12/16/44	7 5½	None None	None None	Mod. Mod.	1a 1a	None None
G.A.	28	Ind.	50	Belgium	1/11/45	1/11/45	5	None	None	Mod.	1c	None

TABLE 1—*Continued*

SUBJECT	AGE	HOME STATE	MONTHS IN SERVICE	WHERE SYMPTOMS BEGAN	DATE ONSET OF SYMPTOMS	DATE OFF LINE	TIME IN MTHS. FROM ONSET TO TIME STUDIED	PREVIOUS FOOT TROUBLE	PREVIOUS TROUBLE WITH TEMP. CHANGES	CLINICAL EVALUATION		AMPUTATIONS
										At onset	At present	
G. R. B.	21	La.	24	Germany	12/10/44	12/15/44	6½	None	Frostbite feet	Mod.	1a	None
J. R. C.	36	Ala.	14	France	11/30/44	11/30/44	7	None	None	Mild	1a	None
H. R. K.	21	Texas	25	Germany	2/25/45	2/ 5/45	4	None	None	Severe	111	All toes both feet.
H. C. J.	25	Ga.	55	Belgium	12/25/44	12/26/44	5½	None	None	Mod.	1a	None
C. A. S.	20	Tenn.	14	Belgium	12/25/44	12/28/44	6	None	None	Mod.	1a	None
J. F. D.	22	N.C.	30	France	11/ 6/44	11/14/44	6½	None	Rt. ft. frostbite	Mod.	1b	None
W. K. W.	33	Miss.	44	Germany	12/10/44	12/11/44	7	None	None	Mod.	1a	None
C. B. H.	33	Ala.	15	France	11/14/44	11/15/44	7½	None	None	Mod.	1a	None
E. J. M.	25	La.	41	Holland	11/ 2/44	11/27/44	7	None	Cramps while swimming	Mild	1a	None
H. L. S.	20	Ala.	26	Germany	1/27/45	1/29/45	6	None	None	Mod.	1a	None
J. C. C.	22	Miss.	16	Italy	2/ 7/45	2/10/45	7	None	None	Mod.	1a	None
H. B.	25	Texas	15	Italy	2/11/45	2/11/45	7	None	None	Mod.	1a	None
C. H. R.	33	La.	34	Germany	1/—/45	12/25/44	5	None	None	Mod.	1a	None
J. D. L.	19	La.	13	Germany	2/—/45	2/—/45	3	None	None	Mod.	1a	None

convalescent patients at the Hospital awaiting discharge, and medical students, technicians, and doctors from the Tulane Medical School. All were known to be in good health and free from any organic disease. None of these patients had had any severe peripheral vascular disease in the past or had suffered from frostbite or any type of injury from cold. These subjects, like the patients with trench foot, were well acquainted with hospital routine and aspects of clinical investigation and tests.

Patients with Psychoneurosis: There were 51 volunteer patients with psychoneurosis. They were from the LaGarde General Hospital and had been under observations for prolonged periods of time, thus offering adequate opportunity of eliminating organic disease. They were all male soldiers varying in age from 19 to 37 years and were transported via ambulance to the Tulane laboratories for study.

Patients with Miscellaneous Vascular Disease States: Several patients with peripheral vascular disease were studied along with those described above. They were divided as follows: three frostbite, one varicose veins, one Raynaud's disease. These few patients were included for orientation purposes.

Almost all of the patients and subjects described above had epidermophytosis of the feet to a mild degree. Subjects with severe epidermophytosis with secondary infection were not studied.

3. Conditions of the Observation Room and Preparation of Patients

a. *Conditions of observation room:* At the onset of the studies it became necessary to choose room conditions obtained by air conditioning apparatus. In order to find the most satisfactory atmospheric conditions, a series of preliminary studies were conducted on normal young adult male subjects and a comparable series of young male soldiers with mild chronic Class I trench foot under room conditions varying in temperature from 14.5°C. (58°F.) to 25.5°C. (78°F.) and relative humidity varying from 50 to 65 per cent. All subjects rested in a comfortable hospital type bed and were nude except for an ordinary type of cotton sheet, which covered their trunks and upper third of the thighs. It was soon found that at temperatures below 18.3°C. (65°F.) most of the normal and trench foot subjects complained of being cold and insisted that they were uncomfortable. Many of

them had a real chill or rigor. At 18.3°C. (65°F.) several subjects had a rigor near the end of the study, which necessitated about 90 minutes stay in the observation room. When room temperatures above 21°C. (70°F.) were used, differences between the normal subjects and those with trench foot, following the reactive hyperemia test (described in detail elsewhere in the paper), were not very great. This was particularly apparent at temperatures of 23.8°C. (75°F.) or higher. When a temperature of 20°C. (68°F.) was used, the subjects found the room pleasantly cool, a sufficient gradient existed between the temperature of the part and that of the room air, to bring out differences in vascular reactions to such stimuli as reactive hyperemia, complete occlusion of arterial and venous circulation of the part, and to nerve block.

It was also found that at a room temperature of 20°C. (68°F.) the relative humidity could vary from 50 to 65 per cent without producing any notable differences in the results. This is of particular importance, since it is difficult, if not impossible, to guarantee a constant relative humidity for prolonged periods of time without a vapor sealed room. The rate of movement of the room air should not exceed 15 feet per minute. Since thermocouples sealed with "Scotch Tape" to the surface of the parts studied measure a temperature on the skin surface determined by a state of equilibrium between the atmospheric temperature and temperature of the part, it was necessary to maintain a constant room temperature, to a variation of less than 0.55°C. (1°F.).

b. *Influence of clothing:* It was noted that if patients were covered with a sheet and woolen blanket (standard type of blanket issued by the U. S. Army) many of the subjects were too warm. Some of them perspired a great deal and showed considerable fluctuations in foot and toe temperatures. In order to standardize the conditions, they were all stripped of their clothing and then covered over the trunk from the shoulders down to include the upper third of the thighs. Under these latter conditions some of the subjects experienced subjective coolness; the large majority were comfortable and enjoyed the atmospheric conditions. None were truly uncomfortable. It is well to emphasize the importance of not varying the amount of clothing. This is well brought out in the studies on the normal females (W. A. C.) in whom the clothing could not be properly controlled.

c. *Weather conditions:* Since it is quite likely that the local weather conditions influence the results of such a study as this, the New Orleans weather during the months of May through September 1945 are summarized in Table 2. These are the warmest months of the year for New Orleans.

d. *Meals:* A series of studies were conducted on subjects with and without the previous meal, that is, the subjects studied in the morning did not eat breakfast and those studied in the afternoon omitted lunch. The subjects who omitted previous meals complained of hunger and showed signs of restlessness and impatience. Since it

TABLE 2

A Summary of the Weather Conditions in New Orleans during the Period of These Studies

TEMPERATURE (°F.)				RELATIVE HUMIDITY (%)		
Month	Mean	Max.*	Min.*	Mean	Max.	Min.
May.....	75.0	83.2	66.7	71.5	96	42
June.....	82.9	91.0	74.8	77.8	98	51
July.....	81.6	87.4	75.7	83.0	99	57
August.....	83.0	89.2	76.7	82.3	99	47
September.....	81.4	88.5	74.3	80.3	98	49
Average for entire period.....	80.8	87.9	73.6	79.0	99	42

* These values are the mean of the extreme temperatures.

was found that the results were not influenced by eating or omitting meals the routine was soon established of permitting all subjects to eat before coming to the laboratory for study. By adopting this routine all patients went from two to three hours without food before observations were begun. Permitting patients to eat at regular Army mess hours simplified the management of the subjects, and avoided the complaints associated with hunger without altering the results.

All subjects were asked not to smoke before the studies, although occasionally we encountered a subject who disobeyed the request. None of them, however, smoked, drank or ate anything once they entered the laboratory for study. Subjects with complicating diseases were not studied.

4. *Description of the Occlusion-Reactive Hyperemia Test*

This procedure was chosen since it was simple to employ and was entirely objective. It was free from any need for cooperation from the subject (except remaining fairly still). It can result in a test of the ability of the vessels of the feet to dilate under intact physiologic conditions. This latter bit of information is important since it is valuable to know some aspects of the ability of the blood vessels of the part to deliver blood to the part to meet requirements of metabolism, thermoregulation and repair. The integration of the functional state of the vessels with the anatomic changes should be observed under the influence of the intact physiologic factors governing the adjustments of the circulation of the part. The test described below gives some indication of these.

The test as employed was as follows:

The subjects entered the observation room, undressed completely, entered a comfortable hospital type bed and were covered with a single cotton sheet from their shoulders to the upper third of the thighs. Blood pressure cuffs with six foot lengths of added cloth were snugly but not tightly wrapped around the lower third of the thighs. These cuffs connected to a metal pressure tank kept automatically at 280 m.m. of Mercury pressure by means of a reduction valve and the air pressure supply of the laboratory. Constantan-copper thermocouples were then placed on five areas, four on each foot commonly showing the most damage from trench foot and one on the middle finger. These points were: (1) the "bunion area"³ (medial aspect of the first metatarsophalangeal articulation); (2) the pad of the terminal portion of the great toe; (3) the pad of the terminal portion of the second toe; (4) the "corn area"³ (lateral aspect of the first interphalangeal articulation of the fifth toe); and (5) the pad of the terminal portion of the middle fingers. By means of a decade switch, each thermocouple was switched into series with a galvanometer and the temperature of the part was measured to within 0.1°C. The temperature of the 10 points was measured continuously *ad seriatum*. When the temperature of all parts reached a fairly constant level (maximum variation in any one part of 0.4°C.), usually requiring

³ These terms are employed for the sake of brevity.

about 30 minutes, *Phase I* of the test was completed. *Phase II*, the *period of occlusion*, of the test was started by sudden occlusion of the arterial and venous circulations by sudden opening of a valve and connecting the cuffs around the legs to the pressure tank. This resulted in cessation of the circulation to the feet without engorgement of the veins and small peripheral blood vessels. The occlusion was maintained for a period of 15 minutes (measured by a stopwatch), the temperature for the ten points being measured continuously *ad seriatum*. *Phase II* was completed and *Phase III*, the *period of reactive hyperemia*, started by the sudden release of the pressure occluding cuffs, by means of valves. The temperatures were still measured for each part *ad seriatum* until a new baseline had been established.

Several aspects concerning this test require comment. For example, a baseline in *Phase I* with a maximum variation for any one of the ten parts of not more than 0.4°C . variation was used instead of an absolute baseline, (1) in order to avoid unduly prolonging the study, (2) because there is usually some fluctuation in the temperature of such parts as a part of the normal fluctuation in vascular blood volume, and (3) such a baseline proved to be satisfactory. A period of 15 minutes of occlusion was chosen, for, as shown by Lewis (6), in occlusions less than 15 minutes duration inadequate amounts of reactive hyperemia result, while occlusions of 20 minutes are associated with a great deal of discomfort with numbness, aching intense tingling and cramping. Occlusions lasting somewhat longer may result in nerve degeneration; occlusion for several hours will result in Volkmann's contractures.

The normal and trench foot subjects were studied at separate times or simultaneously, each in separate adjacent beds.

III. THE EXPERIMENTS

A. The Occlusion-Reactive Hyperemia Test

1. *Normal Subjects and Patients with Trench Foot*: The test was applied to 30 patients with Class I trench foot and 26 normal control subjects. These tests were repeated at least once on each subject for both feet, recording the temperature variations for four areas of each foot and the right middle finger tip of each hand. By using both feet, each foot was a check over the other and resulted in a study of 60 feet with trench foot and 52 normal feet.

The results are summarized by the records shown in Figures 1 through 9. In the normal subjects the typical reaction (Figure 6) consisted of a gradual drop in the temperature of the parts studied during the Phase I period of the test. During Phase II, or the 15 minute period of complete arrest of the circulation, the temperature of the parts decreased very slightly. After release of the circulation there was a rise in temperature (Phase III). This is called a "Normal Reaction."

The patients with trench foot showed quantitative differences. Their reactions were found to vary with the severity of their disease as follows: Patients with Class Ia disease were found to react as the normal control subjects or to show a very slightly greater rise in the temperature of the parts during Phase III of the test (Figure 7). They also tended, at times, to show a slightly greater and more rapid decrease in temperature of the parts during Phase II. The rise during Phase III rarely exceeded 1.5°C . Those patients of Class Ic, more severe disease, reacted in a fashion distinctly different from the normal subjects (Figure 9). They ran higher temperatures of the parts during Phase I, showed a greater and more rapid fall in temperature during Phase II, and decided increase in temperature during Phase III. The rise during Phase III usually was 3°C . or more. This rise tended

FIG. 1. This graph summarizes the temperature recordings for various portions of the feet and tip of the middle fingers in mild chronic trench foot and normal nude subjects covered only from the upper third of the thighs to the shoulders. The subjects remained recumbent at rest in bed in the control room at 20°C . (68°F .), humidity 50 to 65%, and rate of movement of room air less than 15 feet per minute.

B represents the temperature of the part just before occlusion of the circulation to the feet.

O represents the temperature of the part at the end of 15 minutes of occlusion of the circulation to the feet.

R represents the maximum temperature reached by the part after release of the circulation.

Thirty subjects (15 normal and 15 with Class I trench foot, 7 Class Ia, 3 Class Ib and 5 Class Ic). These studies represent single measurements on each subject during one week.

The mean values are shown within the columns. The extreme values are in the parenthesis above each column. This scheme of labeling is employed in the figures throughout.

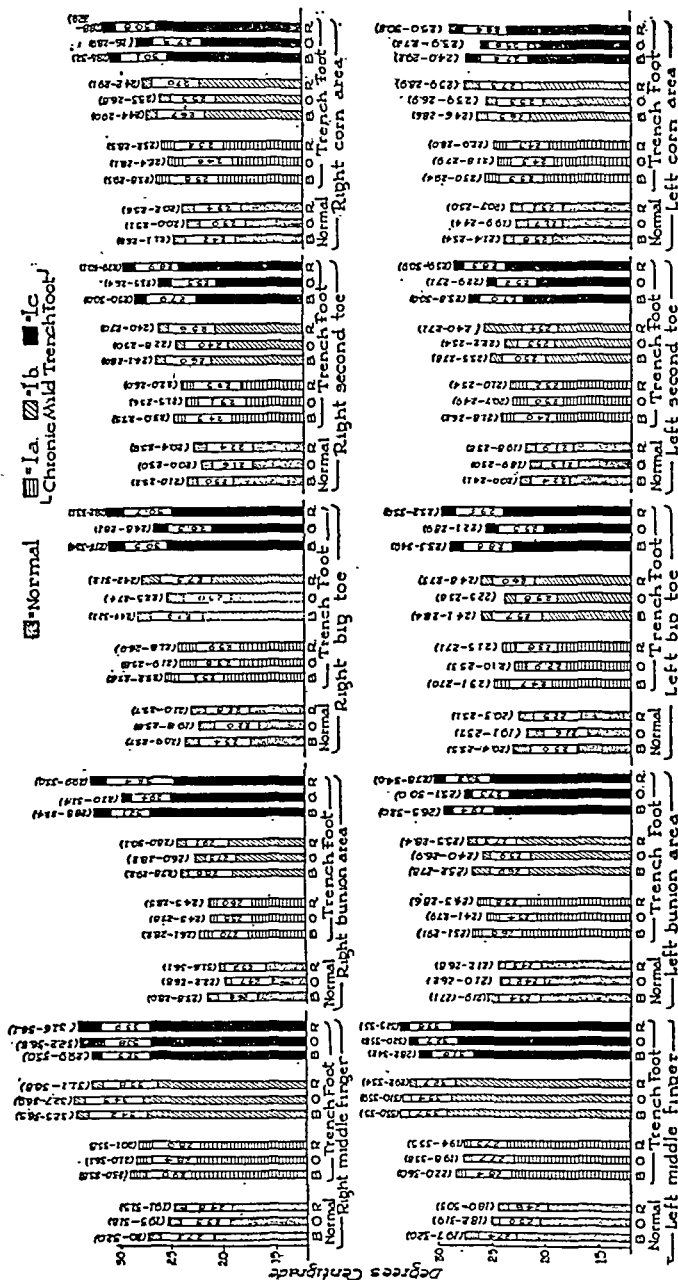


Fig. 1

to show a direct relationship to the degree and duration of the reactive hyperemia (*vide infra*). Those patients with Class Ib trench foot presented reactions and temperature curves which were between those of Class Ia and Ic. Of the 30 patients with trench foot, 16 showed the Class Ia reaction, 5 the Class Ib and 4 the Class Ic reactions. All 26 normal subjects had the normal or Class Ia type reaction.

Each individual patient or subject consistently presented the same type of reaction each time studied.

The differences in the reactions to the occlusion-reactive hyperemia test are illustrated by Figures 1 through 9 and Table 3. Figures 1 and 4 include the results for one week of study, while Figures 2 and 5 show the results for an entire series of observations over a period of several weeks. There are no differences in the nature of the reactions if tracings of an individual subject, tracings of a small group of subjects or tracings of a large series are examined. The reactions just mentioned were studied at a room temperature of 20°C. (68°F.). They were not different from some recorded at a room temperature of 18.3°C. (65°F.) (Figures 10 and 11). It can be seen from Table 3 that some of the temperature differences have mean values which are not statistically significant. This is most probably the result of the lack of a sufficiently large number of subjects in each series.

2. *Patients with Trench Foot and Patients with Psychoneurosis:* In order to further check the results just described, 24 of the above 30

FIG. 2. This graph summarizes the temperature recordings for various portions of the feet and tip of the middle fingers in mild chronic trench foot and normal nude subjects covered only from the upper third of the thighs to the shoulders. The subjects remained recumbent at rest in bed in the control room at 20°C. (68°F.), humidity 50 to 65%, and rate of movement of room air less than 15 feet per minute.

B represents the temperature determinations of the part just before occlusion of the circulation to the feet.

O represents the temperature of the part at the end of 15 minutes of occlusion of the circulation to the feet.

R represents the maximum temperature reached by the part after release of the circulation to the feet.

Eighty-five observations were made on 26 normal and 30 Class I trench foot subjects. The studies were conducted over a period of several weeks and represent 2 or more determinations on each subject.

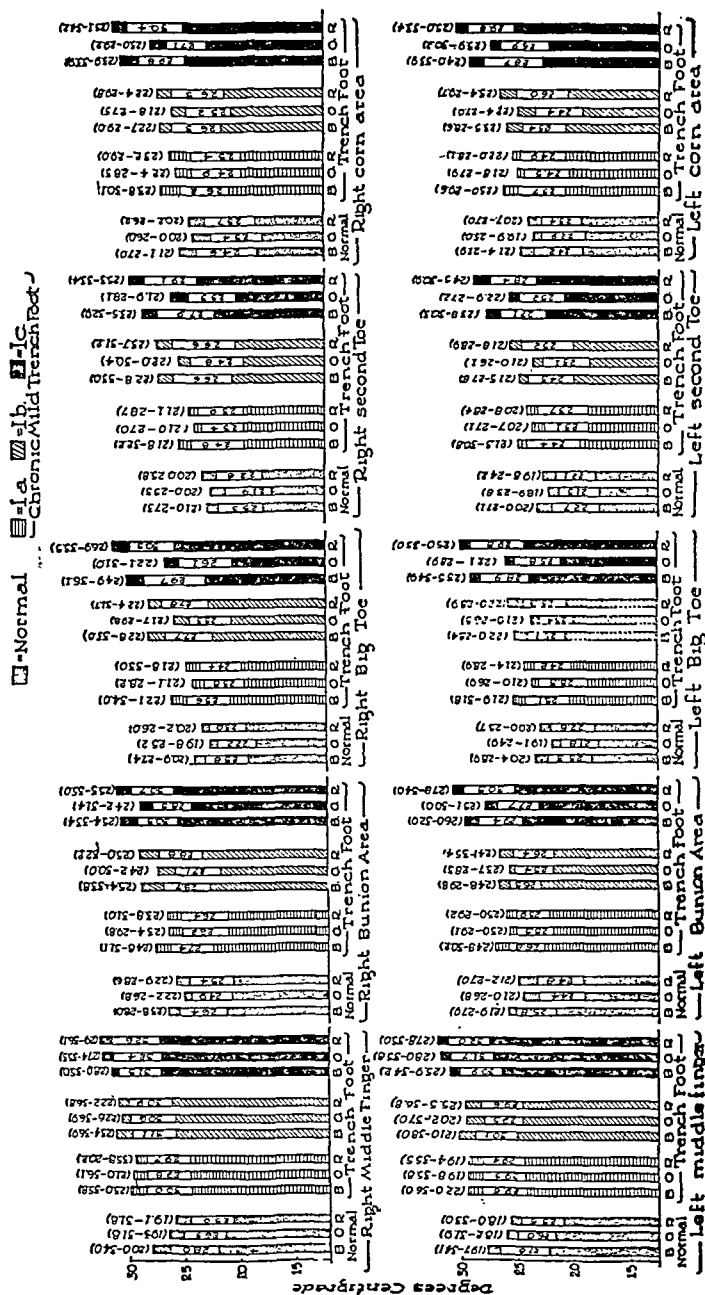


Fig. 2

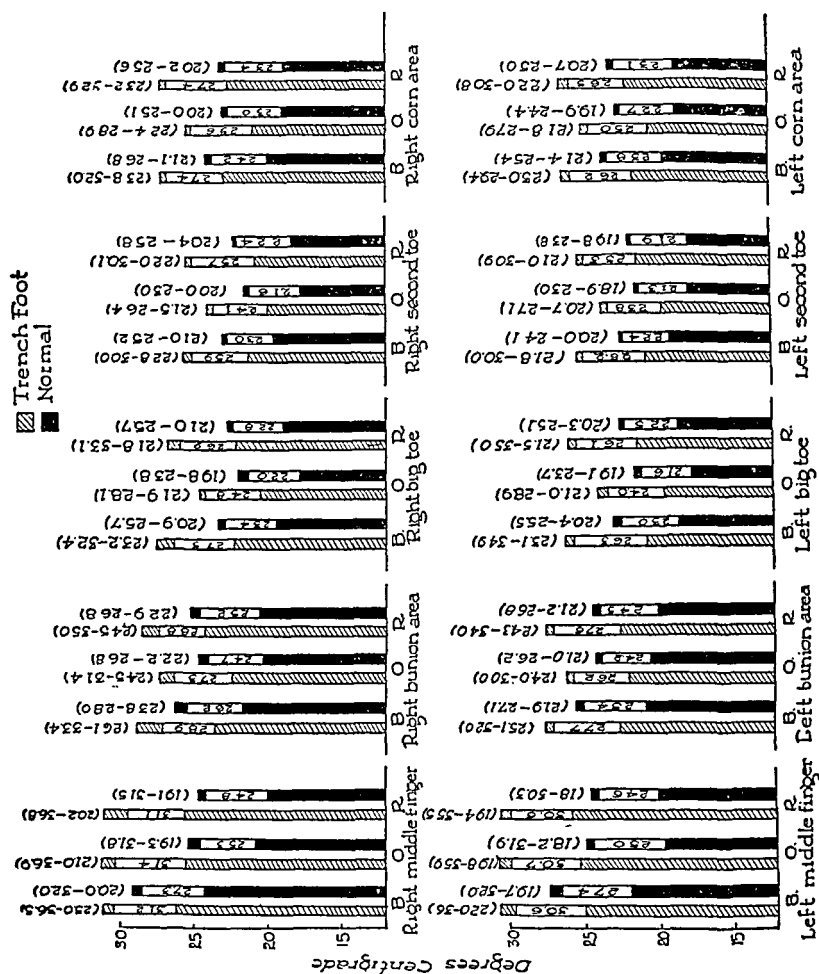


FIG. 3. This graph summarizes the temperatures recorded for various portions of the feet and the tip of the middle fingers of normal and Class I trench foot subjects shown in Figure 1. The prevailing conditions were identical to those in Figures 1 and 2.

This graph shows the differences between the normal and trench foot subjects, both as to absolute values in temperature and variations brought about by the three phases of the occlusion-reactive hyperemia test.

patients with trench foot were subjected simultaneously with 38 patients with psychoneurosis to the occlusion-reactive hyperemia

test applied to the right arm of each subject. A patient with each condition rested in separate adjacent beds. The experimental conditions were precisely the same as for the study of normal and trench foot subjects just described. Each trench foot patient was studied twice, with a different control patient with psychoneurosis.

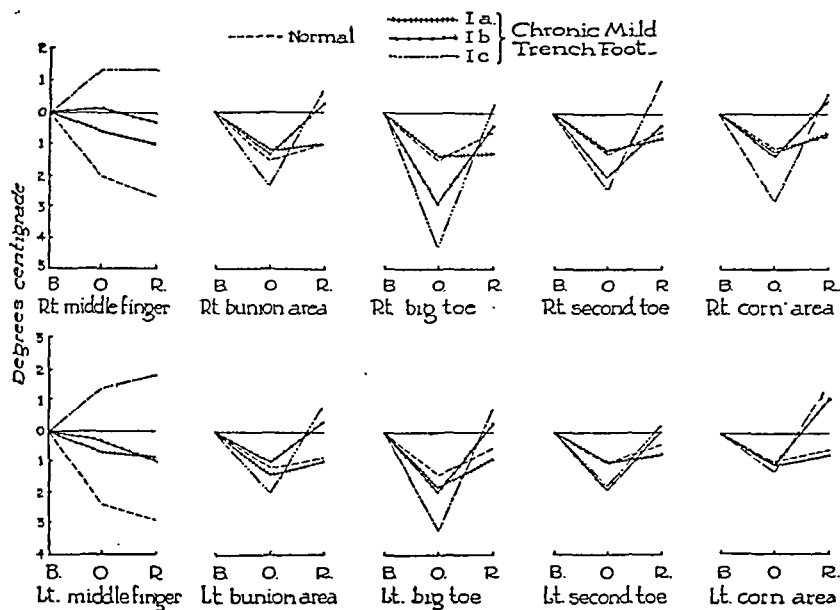


FIG. 4. This graph shows only the changes in temperature for the various parts during the occlusion-reactive hyperemia test in normal subjects and patients with trench foot, Class I (subgroups indicated). The zero temperature or reference value is that temperature noted just before occlusion of the circulation. The graph represents the changes in temperatures shown in Figure 1 without noting the absolute temperature values.

During these studies the finger and toe tip temperature variations were observed simultaneously during the occlusion-reactive hyperemia test. Temperature measurements were made on the: (1) tip or pad of the right index finger; (2) tip or pad of the right middle finger; (3) tip or pad of the right big toe; (4) tip or pad of the right second toe; and (5) tip or pad of the left middle finger of both patients with trench foot and those with psychoneurosis. During Phase II of the test, the circulation of the right arm and right leg were completely

occluded simultaneously by suddenly increasing the pressure in blood pressure cuffs applied to the right arm and right thigh above the elbow and knee, respectively.

The results are summarized by Figures 12 and 13 and 14. These Figures show a slight difference between the subjects with psychoneurosis and those with trench foot. Although these 38 patients

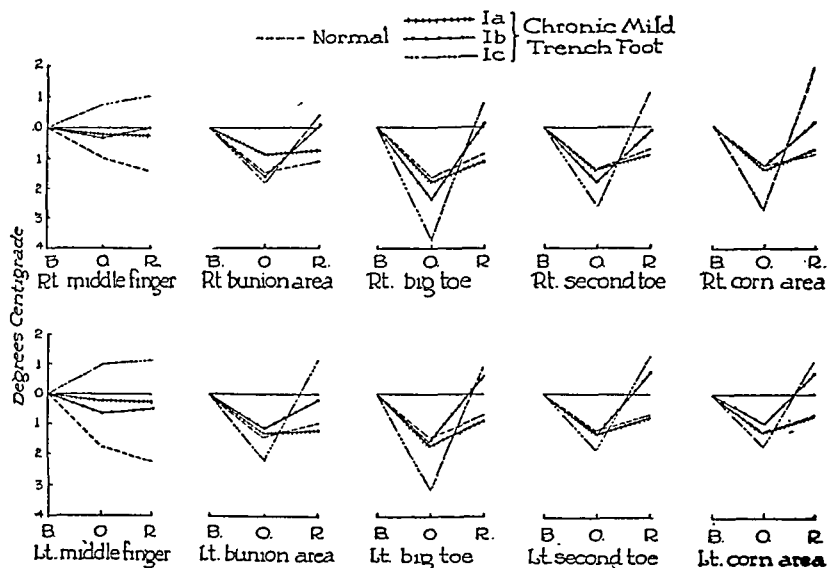


FIG. 5. This graph represents the changes in temperature of the various parts during the occlusion-reactive hyperemia test in normal subjects and patients with Class I trench foot. The zero or reference temperature is that recorded just before occlusion of the circulation to the feet. The graph represents the changes in temperature shown in Figure 2 without noting the absolute temperature values.

were supposed to have uncomplicated psychoneurosis, one had had trench foot in November, 1944, two had marked epidermophytosis of the feet with secondary infection, one was recuperating from the severe type of fungus infection of the feet contracted in the Southwest Pacific area ("Jungle Rot"), one was receiving atabrine, and several had received bullet wounds affecting the limbs (one of the right foot, one of the knee, one of the lumbar vertebrae, and one of the right hand). These wounds were essentially but not completely without

symptoms. Several of these subjects reacted to the occlusion-reactive hyperemia test as the Class Ia or Class Ib trench foot subjects. This

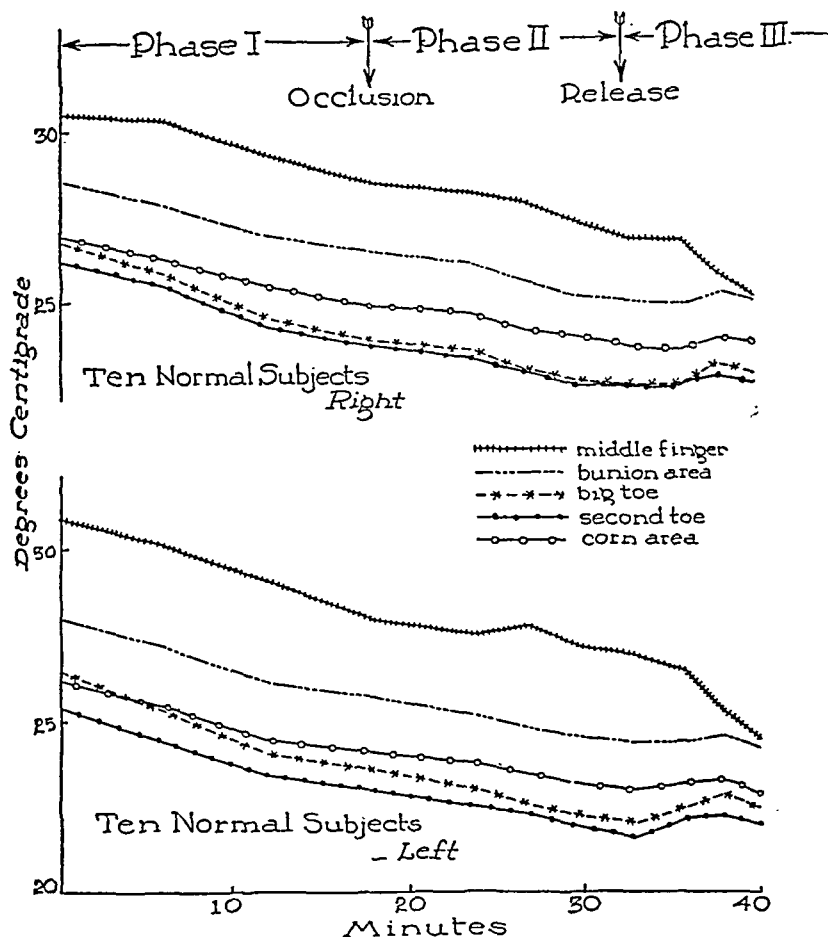


FIG. 6. Tracings of the occlusion-reactive hyperemia test for the right and left feet. Each tracing represents a composite of recordings for ten normal subjects.

See text for description of occlusion-reactive hyperemia test and other details of the reactions.

was particularly true of those patients with the fungus infections of the feet and the patient who had had trench foot. None of these subjects, however, showed as marked a reaction as the Class Ic chronic

trench foot patient. All patients with psychoneurosis, regardless of the presence or absence of complications, were included in compiling

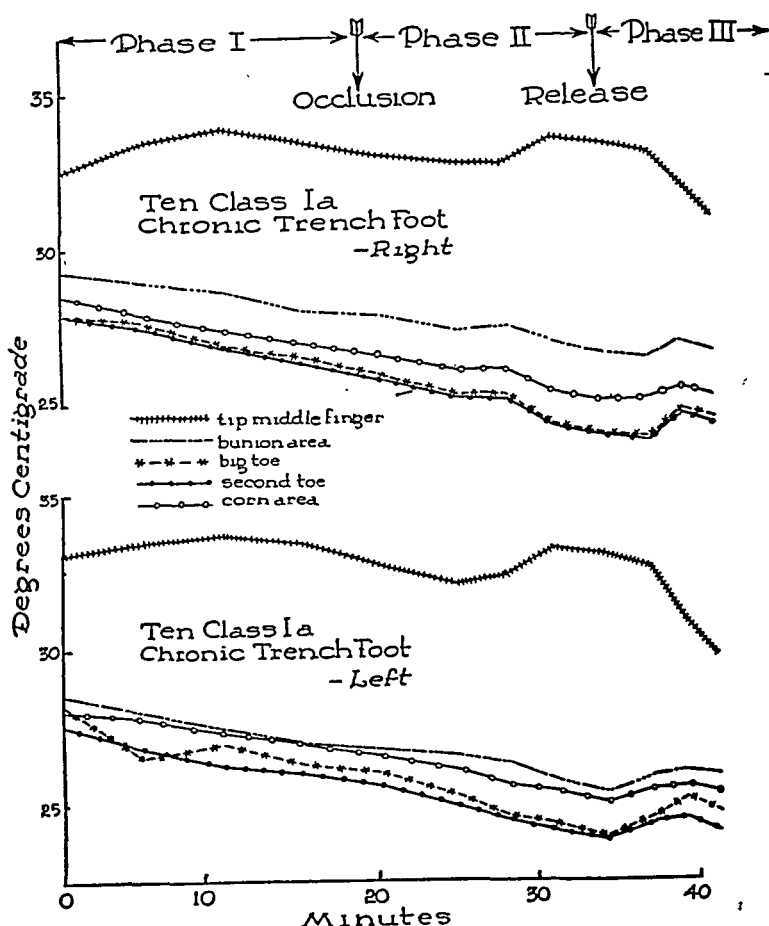


FIG. 7. Tracings of the occlusion-reactive hyperemia test for the right and left feet. Each tracing represents a composite of recordings for ten Class Ia trench foot subjects.

See text for description of occlusion-reactive hyperemia test and other details of the reaction.

Figures 13 and 14. If those patients with the complicating states were excluded, the differences between the patients with Ib or Ic trench foot and those with psychoneurosis would be greater. In the

construction of Figure 14, those patients with psychoneurosis who had the complications mentioned above were not used.

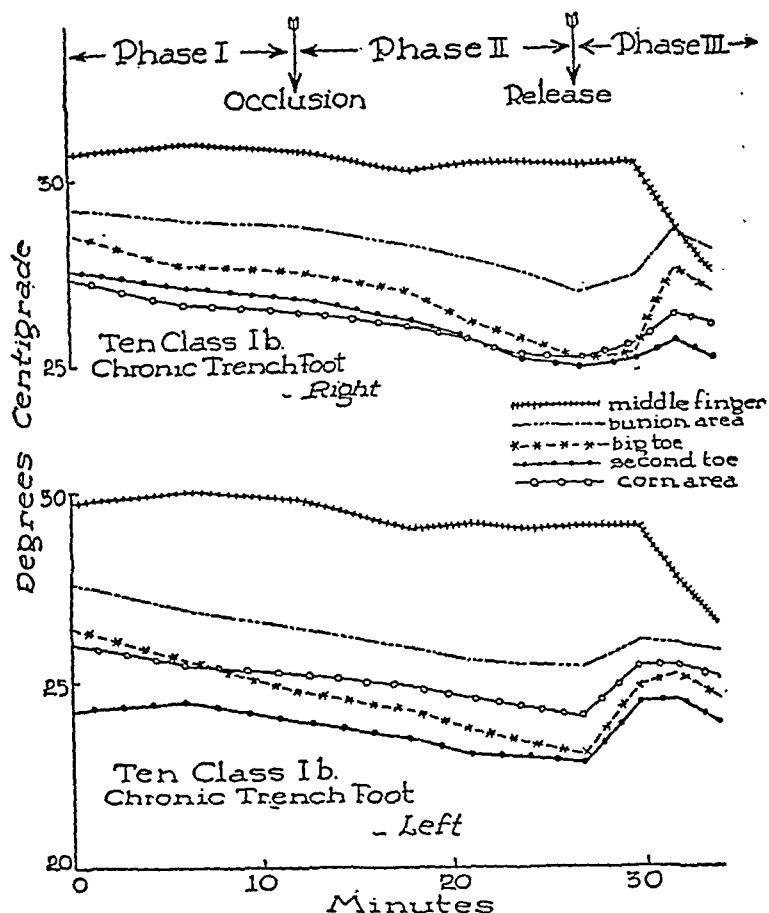


FIG. 8. Tracings of the occlusion-reactive hyperemia test for the right and left feet. Each tracing represents a composite of recordings for ten Class Ib trench foot subjects.

See text for description of occlusion-reactive hyperemia test and other details of the reaction.

In the finger tips of both the patients with trench foot and the patients with psychoneurosis there was a sharp drop after occlusion and a rise after release which did not attain the Phase I temperature

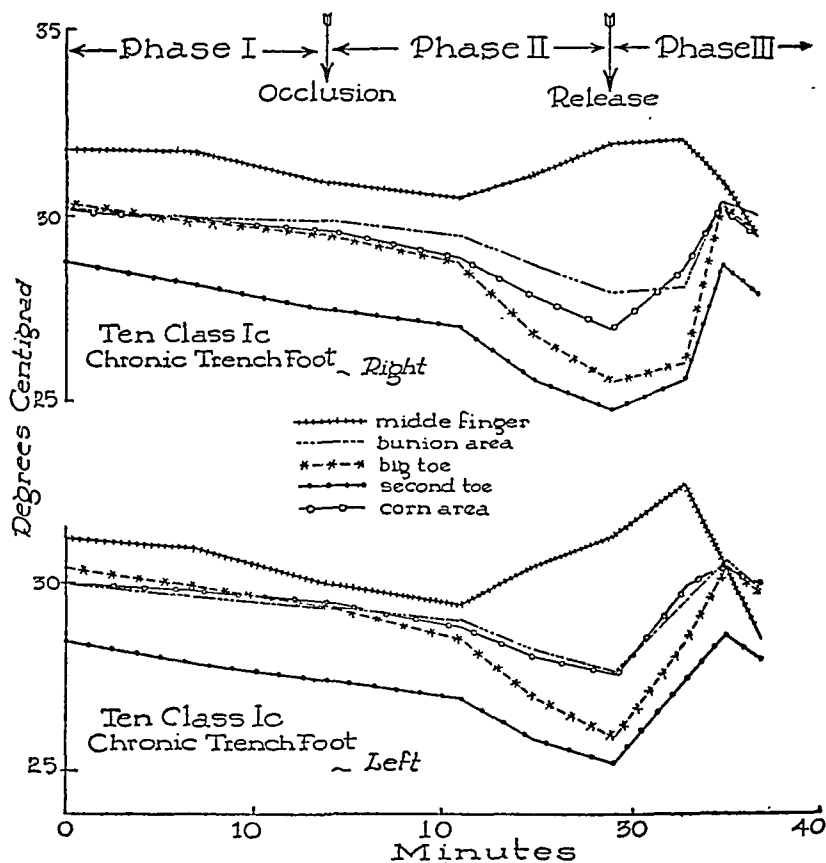


FIG. 9. Tracings of the occlusion-reactive hyperemia test for the right and left feet. Each tracing represents a composite of recordings for Class Ic trench foot subjects.

See text for description of occlusion-reactive hyperemia test and other details of the reactions.

levels. This marked drop is probably the result of the marked difference between the finger tip and room temperature, while in the toes, when this marked temperature gradient did not exist, the temperature

FIG. 10. This graph summarizes the temperature values for various portions of the feet and the tip of the middle fingers of 10 normal and 16 Class I trench foot (8 Class Ia, 3 Class Ib, and 5 Class Ic) subjects. All conditions prevailed as for Figures 1 and 2 except that the room was slightly colder, 18.3°C. (65°F.).

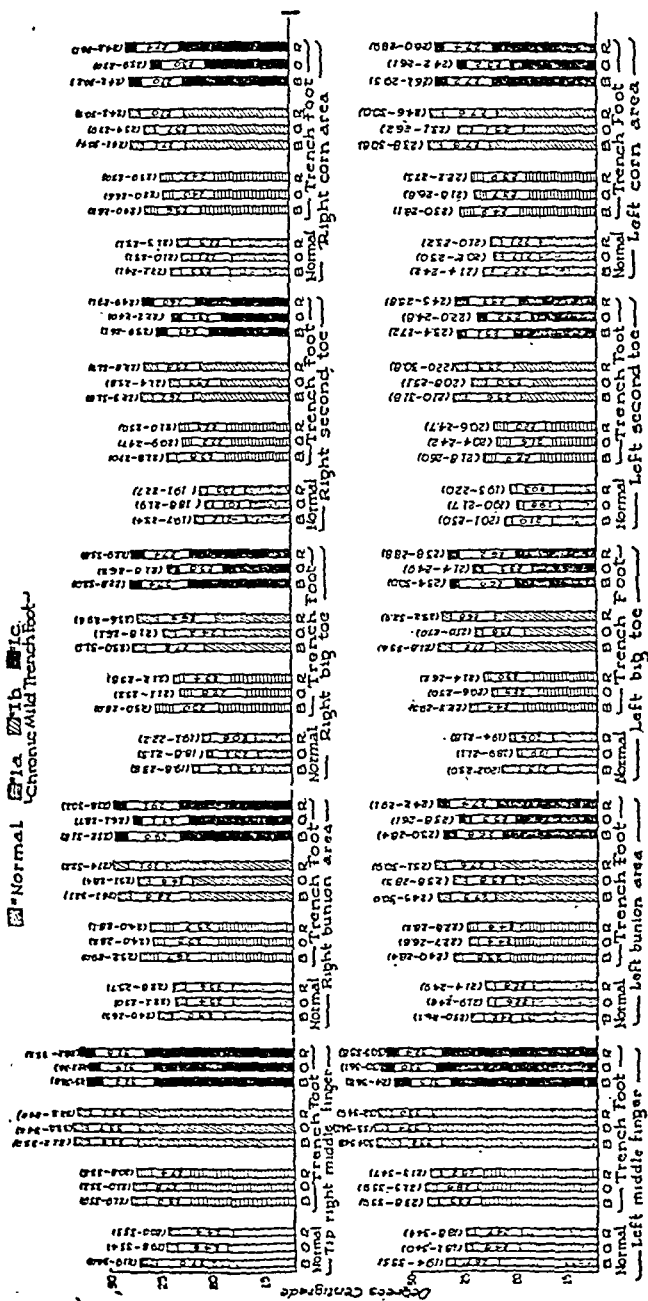


Fig. 10

TABLE 3

The Change in Temperature of Various Portions of the Feet and Tip of the Right Middle Finger Following the Occlusion-Reactive Hyperemia Test
 Statistical constants are shown for patients with mild chronic trench foot and normal subjects. All temperature values are in degrees centigrade.

	MIDDLE FINGER				DUNION AREA				TIP BIG TOE				TIP SECOND TOE				CORN AREA			
	Mean	Range	Stand- ard deviation	Coeffi- cient varia- tion %	Mean	Range	Stand- ard deviation	Coeffi- cient varia- tion %	Mean	Range	Stand- ard deviation	Coeffi- cient varia- tion %	Mean	Range	Stand- ard deviation	Coeffi- cient varia- tion %	Mean	Range	Stand- ard deviation	Coeffi- cient varia- tion %
Normal																				
Temp. before occlusion	28.18 ±0.9	20 to 34	7.0 ±0.7	24.9 ±2.5	26.5 ±0.4	23.8 to 28	2.8 ±0.3	10.5 ±1.0	24.1 ±0.3	20.9 to 27.4	2.6 ±0.2	10.8 ±1.0	23.4 ±0.2	21 to 27.3	1.8 ±0.2	7.7 ±1.1	25.7 ±0.4	21.1 to 27	3.0 ±0.3	11.7 ±1.1
Temp. end of occlusion	26.5 ±0.9	19.3 to 31.8	6.6 ±0.6	24.9 ±2.5	25.0 ±0.3	22.2 to 26.8	2.0 ±0.2	8.0 ±0.8	22.3 ±0.3	19.8 to 25.2	2.6 ±0.2	11.7 ±1.1	22.2 ±0.2	20 to 25.3	1.6 ±0.2	7.2 ±0.7	23.6 ±0.4	20 to 26	2.9 ±0.3	12.3 ±1.2
Change in temp.	4.4 ±0.9	-6.0 to +4	2.9 ±0.6	58.3 ±7.1	-1.5 ±0.1	-0.6 to -3.9	0.6 ±0.1	37.7 ±0.4	-1.8 ±0.1	-0.9 to -4.2	0.7 ±0.1	103.0 ±17.0	8.2 ±0.2	-0.5 to -3.1	1.4 ±0.1	17.1 ±1.6	-1.3 ±0.1	-0.5 to -1.8	0.7 ±0.06	51.5 ±6.0
Max. temp. after release	26.0 ±0.9	+2.1 to 31.8	6.8 ±0.6	26.2 ±2.6	25.4 ±0.3	22.9 to 28.6	2.5 ±0.2	9.8 ±1.0	23.0 ±0.4	20.2 to 26	2.8 ±0.3	12.1 ±1.2	22.7 ±0.3	20 to 25.8	2.2 ±0.2	9.7 ±1.0	23.8 ±0.4	20.2 to 26.2	3.1 ±0.3	13.0 ±1.2
Change in temp. after release	3.4 ±0.3	-1.6 to +2.1	2.4 ±0.2	71.6 ±9.6	4.4 ±0.2	-0.4 to +2.8	1.5 ±0.1	33.9 ±3.2	+0.8 ±0.1	0 to -2.9	1.5 ±0.1	93.2 ±0.9	3.8 ±0.2	-0.1 to +1.6	1.2 ±0.1	31.9 ±3.3	+0.4 ±0.04	-0.1 to +0.9	0.3 ±0.03	84.9 ±12.5
LEFT FOOT																				
Temp. before occlusion	27.8 ±1.1	19.7 to 34.1	7.8 ±0.8	28.0 ±2.9	25.5 ±0.4	21.9 to 27.9	3.3 ±0.3	13.0 ±1.2	23.4 ±0.4	20.4 to 28.9	2.8 ±0.3	11.5 ±1.1	22.7 ±0.3	20 to 27.1	2.2 ±0.2	9.7 ±1.0	24.3 ±0.3	21.4 to 27.9	2.6 ±0.2	10.7 ±1.0
Temp. end of occlusion	26.0 ±1.1	18.2 to 31.9	8.2 ±0.8	31.5 ±3.3	24.6 ±0.3	21 to 26.8	2.1 ±0.2	8.6 ±0.8	21.8 ±0.3	19.1 to 24.9	2.1 ±0.2	9.6 ±0.9	21.6 ±0.2	18.9 to 23.8	1.6 ±0.2	7.4 ±0.7	23.7 ±0.4	19.9 to 25	3.1 ±0.3	13.0 ±1.2
Change in temp.	11.1 ±0.8	-6.5 to +3.1	4.7 ±0.5	42.0 ±4.1	0.6 ±0.1	-0.7 to -2.0	0.1 ±0.1	1.7 ±0.2	-1.6 ±0.2	-0.7 to -2.2	1.4 ±0.1	90.3 ±13.8	3.4 ±0.1	-0.3 to -3.3	1.8 ±0.1	26.3 ±2.6	-1.3 ±0.1	-0.4 to -3.7	1.3 ±0.1	51.9 ±5.3
Max. temp. after release	22.5 ±1.0	18 to 33	7.2 ±0.7	32.0 ±3.3	24.8 ±0.4	21.2 to 27	3.1 ±0.3	12.5 ±1.2	22.7 ±0.3	20 to 25.7	2.2 ±0.2	9.7 ±0.9	22.3 ±0.2	19.8 to 24.2	1.6 ±0.2	7.2 ±0.7	23.4 ±0.4	20.7 to 27	2.7 ±0.3	11.5 ±1.1
Change in temp. after release	3.6 ±0.2	-3.0 to +2.1	1.7 ±0.2	46.7 ±5.3	2.4 ±0.1	-0.2 to +1.8	0.8 ±0.1	30.6 ±2.9	+0.8 ±0.1	0 to +2.5	0.7 ±0.1	90.2 ±6.9	3.4 ±0.2	-0.2 to +1.8	1.4 ±0.1	41.8 ±4.6	2.9 ±0.1	-0.2 to +2.8	0.7 ±0.1	23.7 ±2.3

Trench foot

RIGHT FOOT	31.2	21.7 to	9.0	28.8	31.4	21.2 to	9.3	29.6	26.5	21.8 to	4.9	18.5	25.9	21.3 to	4.2	16.2	31.3	21 to	9.1	29.1
Temp. before occlusion	± 0.9	38.8	± 0.6	± 2.1	± 0.9	38.3	± 0.7	± 2.2	± 0.5	36.8	± 0.3	± 1.3	± 0.4	36	± 0.3	± 1.1	± 0.9	38	± 0.6	± 2.5
Temp. end of occlusion	25.9	20.2 to	5.5	21.2	26.2	20 to	5.7	21.8	24.2	20.8 to	3.5	14.5	23.9	20.8 to	3.7	15.4	30.4	20 to	10.3	34.0
	± 0.5	32.8	± 0.4	± 2.07	± 0.6	32.3	± 0.4	± 1.6	± 0.3	31.1	± 0.2	± 1.2	± 0.4	29.2	± 0.3	± 1.5	± 1.0	38.8	± 0.7	± 2.5
Change in temp.	5.37	+0.2 to	4.0	74.5	5.8	-1.0 to	5.6	97.4	3.2	+0.5 to	2.5	81.8	1.8	-2 to	1.8	102.8	11.0	-3.0 to	5.3	48.0
	± 0.4	8.9	± 0.3	± 7.5	± 0.5	8.0	± 0.4	± 11.4	± 0.2	8.2	± 0.2	± 8.6	± 0.2	4.7	± 0.1	± 7.8	± 0.5	+5.0	± 0.4	± 4.0
Max. temp. after release	28.2	21.3 to	6.4	22.7	28.4	20.8 to	7.7	27.1	25.8	21.8 to	4.7	18.2	25.3	21.4 to	4.3	17.0	30.4	20 to	9.5	31.3
	± 0.6	34.1	± 0.4	± 1.6	± 0.8	34	± 0.5	± 2.0	± 0.5	34.9	± 0.3	± 1.3	± 0.4	32.1	± 0.3	± 1.1	± 0.9	37.9	± 0.7	± 2.4
Change in temp. after release	11.1	-0.2 to	4.1	36.9	2.5	0 to	2.1	83.3	1.7	0 to	1.3	76.9	1.2	0 to	2.9	239	5.0	-2.7 to	2.1	42.0
	± 0.4	+7.2	± 0.3	± 2.9	± 0.2	+7.2	± 0.1	± 8.9	± 0.1	+0.5	± 0.8	± 7.9	± 0.3	+4.6	± 0.2	± 17.3	± 0.2	+2.4	± 0.1	± 3.4

Patients with psychoneurosis

RIGHT FOOT	30.5	21.2 to	9.0	29.5	30.2	21.3 to	8.5	28.2	25.2	20.7 to	4.0	15.9	24.6	20.4 to	3.6	14.6	29.8	21.0 to	9.2	30.8
Temp. before occlusion	± 0.9	41.9	± 0.6	± 2.2	± 0.8	41.9	± 0.6	± 3.1	± 0.4	35.2	± 0.3	± 1.1	± 0.3	36.2	± 0.3	± 1.0	± 0.9	42.4	± 0.6	± 2.3
Temp. end of occlusion	25.8	20.7 to	4.8	18.6	25.9	20.8 to	5.6	21.6	22.9	19.8 to	4.0	17.4	23.3	19.9 to	3.8	15.9	30.4	20.8 to	9.8	32.3
	± 0.5	35.0	± 0.3	± 1.3	± 0.5	36.0	± 0.5	± 1.5	± 0.4	29.1	± 0.3	± 1.2	± 0.4	28.8	± 0.3	± 1.1	± 1.0	41.9	± 0.7	± 2.5
Change in temp.	7.6	-0.3 to	5.9	77.7	6.2	-0.1 to	5.8	81.0	2.0	-0.1 to	1.6	80.0	1.4	-0.2 to	1.0	71.8	5.9	-4.1 to	6.3	90.4
	± 0.6	8.9	± 0.4	± 8.0	± 0.6	8.2	± 0.4	± 8.5	± 0.2	-7.2	± 0.1	± 6.0	± 0.1	-7.4	± 0.1	± 7.1	± 0.6	+6.0	± 0.4	± 6.7
Max. temp. after release	29.0	21.6 to	7.2	24.8	29.2	21.5 to	7.6	24.3	25.8	21.0 to	3.4	24.1	24.7	21.0 to	3.4	13.8	27.8	21.6 to	8.4	28.2
	± 0.7	40.0	± 0.5	± 1.9	± 0.7	40.9	± 0.5	± 1.8	± 0.3	36.9	± 0.2	± 1.7	± 0.3	35.0	± 0.2	± 1.0	± 0.8	40.8	± 0.6	± 3.2
Change in temp. after release	3.4	+0.1 to	4.0	91.9	5.3	-1.8 to	4.7	88.9	2.1	0 to	1.8	84.5	1.7	-0.1 to	1.7	7.1	1.8	-1.9 to	1.1	62.7
	± 0.4	8.0	± 0.3	± 10.4	± 0.5	+8.3	± 0.3	± 9.8	± 0.2	+7.8	± 0.1	± 8.8	± 0.2	+6.2	± 0.1	± 0.5	± 0.1	+4.1	± 0.1	± 5.8

changes were not nearly so great. These differences in initial levels of the finger tips and toe tips is an expression of differences at least in their local circulations. The finger, with its known extensive vascularity and many glomi, would be expected to have a higher temperature.

These differences probably explain the marked rise in the temperature of the finger-tip after release with the only relatively slight rise

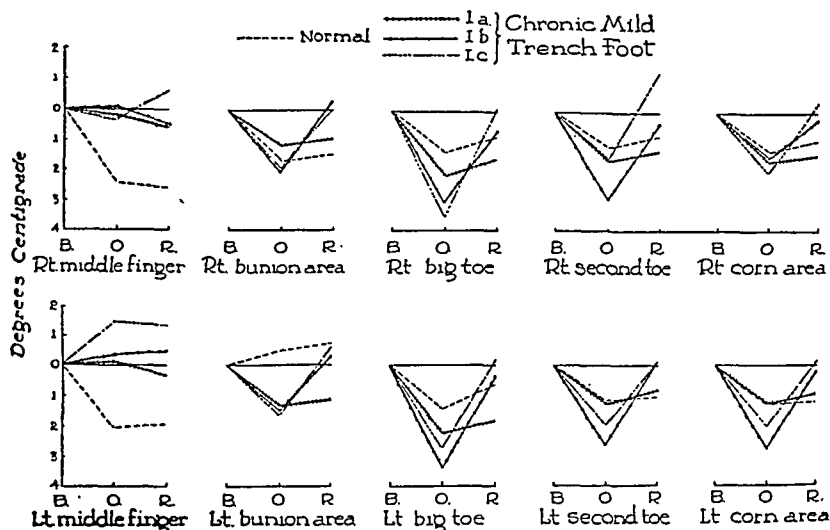


FIG. 11. This graph represents only the changes in temperature for the parts during the occlusion-reactive hyperemia test shown in Figure 10. The zero value or reference temperature is that noted just before occlusion of the circulation to the feet. Absolute values are not indicated.

in the temperatures of the toes. The qualitative nature of the reactions in the finger and toe tips were the same, however.

3. *Posterior Tibial Nerve Block*: Posterior tibial nerve block was employed to eliminate, for all practical purposes, nervous control of the vessels in the foot. Temporary blocking of the posterior tibial nerve with procaine at the lower border of the medial malleolus obtained a warm, dry foot with anesthesia of the sole in the cutaneous distribution of the medial and lateral plantar nerves, terminal branches of the posterior tibial nerve. This nerve block removed vasoconstrictor influences initiated by psychogenic, reflex and environmental

stimuli. Thus an opportunity was provided for study of circulatory responses uninfluenced by nervous control. Vasospasm was eliminated, and almost complete potential blood flow to the plantar portions of the foot was attained and evaluated. Although posterior tibial nerve block falls short of complete obliteration of nervous

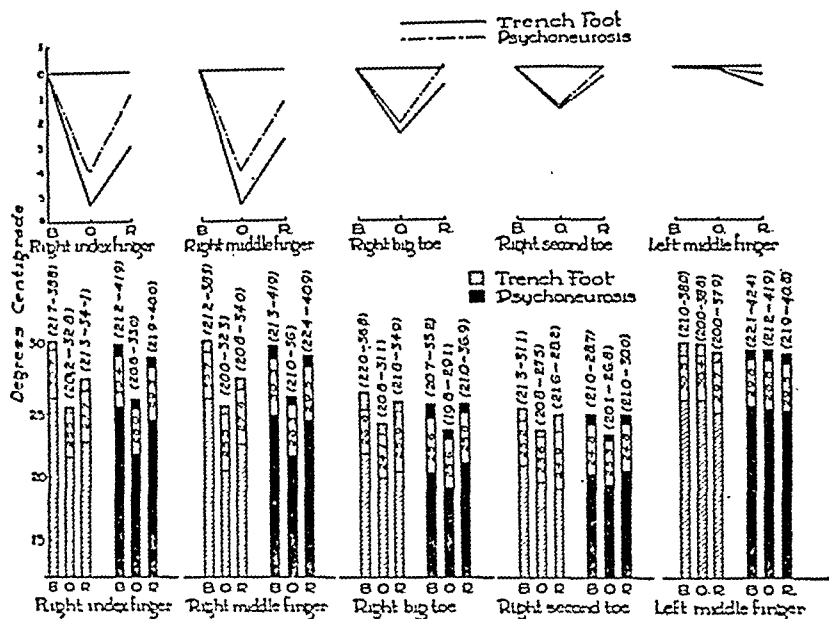


FIG. 12. This graph summarizes the temperature observations made before, during occlusion and after release of the circulation of the right foot and right hand. Trench foot and psychoneurotic subjects are compared. The graph shows both the absolute values (lower column graph) and the changes in temperature only (upper line graphs). Consult the text for details.

There were 29 patients of whom 18 were psychoneurotic and 11 had trench foot. They were studied during a single week.

vasoconstriction and is inferior to spinal anesthesia or lumbar sympathetic block for that purpose, the ease and simplicity of this procedure offset the failure to obtain complete removal of all vasoconstriction. Lumbar sympathetic block has the additional advantage of producing no anesthesia in the foot and no motor paralysis in some of the intrinsic muscles in the sole of the foot. The features of anesthesia of the sole of the foot in the distribution of the medial and lateral plantar nerves

and paralysis of some of the intrinsic muscles in the sole of the foot interfere slightly with walking for the duration of action of the anesthetic agent used in blocking. Simultaneous bilateral blocking is therefore not advised.

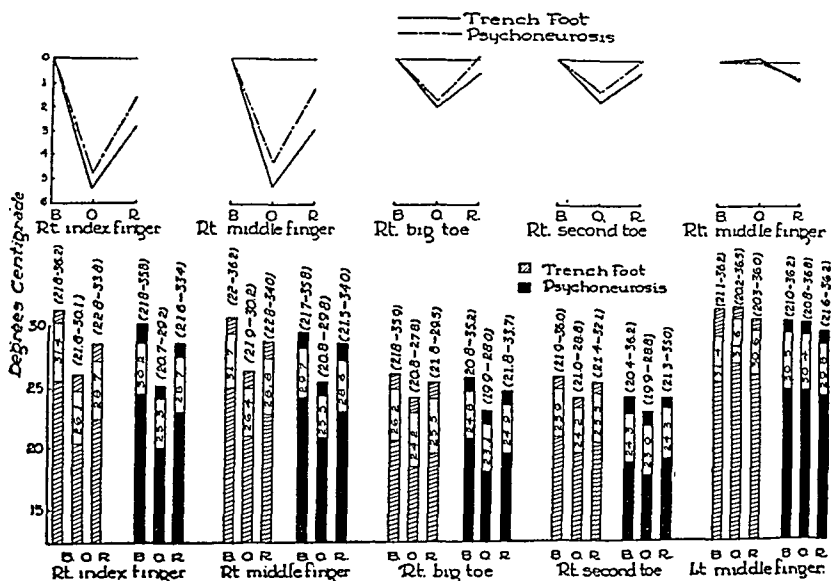


FIG. 13. This graph summarizes the temperature observations made before during occlusion and after release of the circulation of the right foot and right hand. The graph shows both the absolute values (lower column graph) and the changes in temperature only (upper line graphs). Consult the text for details. Trench foot and psychoneurotic subjects are compared.

There were 76 observations upon 62 subjects of whom 38 had psychoneurosis and 24 had trench foot. They were studied over a period of several weeks, most of them being studied at least twice.

The method used in producing the posterior tibial nerve block: The skin was prepared with a suitable antiseptic (denatured 70 per cent alcohol). A point was selected at the junction of the anterior third and posterior two thirds of a line drawn from the center of the medial malleolus to the junction of the plantar and posterior point of the heel. A wheal was produced with 1 cc. of 2 per cent procaine at this point with a small syringe and 24 gauge hypodermic needle.

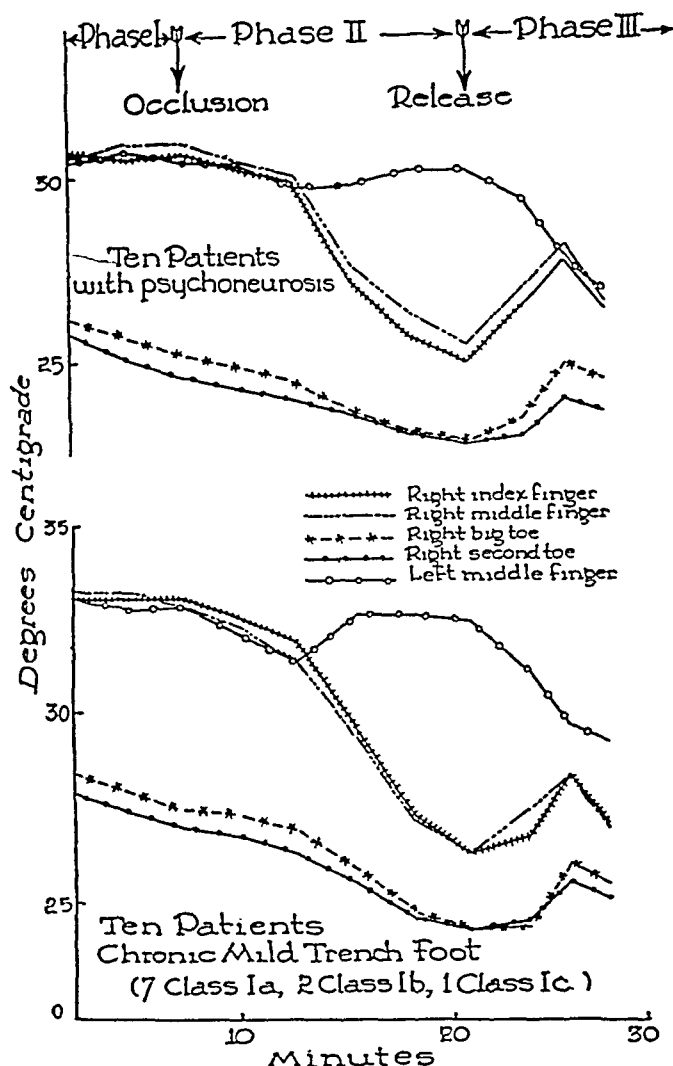


FIG. 14. Temperature observations before, during and after release of occlusion of the circulation of both upper and lower right extremities. These tracings represent a composite of the curves of 10 psychoneurotic patients and 10 trench foot patients.

A 19 gauge needle was then introduced perpendicularly through the anesthetized skin down to the bone and 10 cc. of 2 per cent procaine

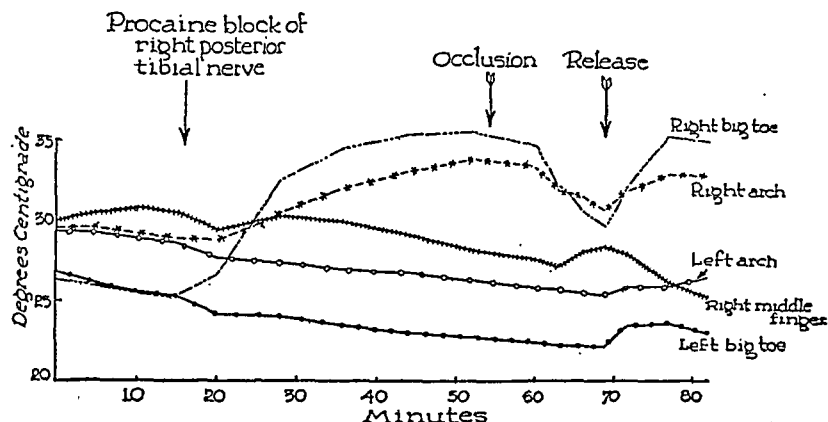


FIG. 15. Temperature observations of the combined effects of posterior tibial nerve block and the occlusion-reactive hyperemia test. Only the right posterior tibial nerve was blocked in each case. The occlusion-reactive hyperemia test was applied to both feet, not to the hands.

These curves represent the composite recordings of 10 normal male subjects.

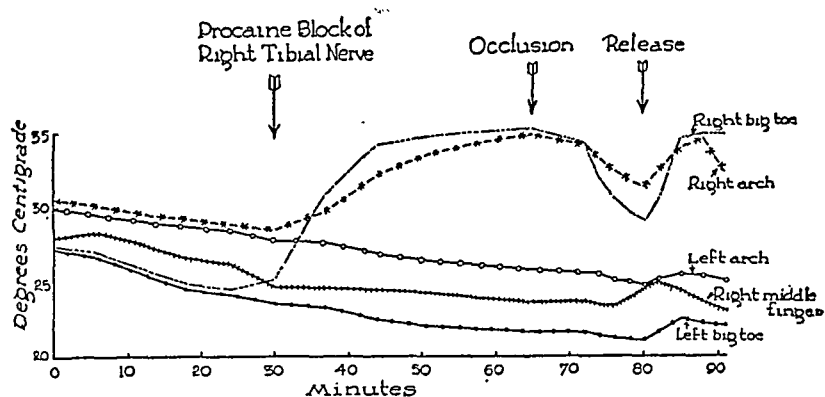


FIG. 16. Temperature observations of the combined effects of posterior tibial nerve block and the occlusion-reactive hyperemia test. Only the right posterior tibial nerve was blocked in each case. The occlusion-reactive hyperemia test was applied to both feet, not to the hands.

These curves represent the composite recordings of 10 normal female subjects.

was injected. Within 15 to 30 minutes the maximum effect was reached as measured by (1) anesthesia of the sole of the foot in the cutaneous distribution of the medial and lateral plantar nerves; (2)

a definite rise in temperature and (3) a cessation of local sweating. The full effect was maintained for approximately one hour with a gradual decline during the next hour.

Application of posterior tibial nerve block to circulatory studies: Studies similar to those described above were conducted upon 12 subjects with Class Ia trench foot, 12 patients with psychoneurosis, 19 male normal subjects and 19 normal females. The only new

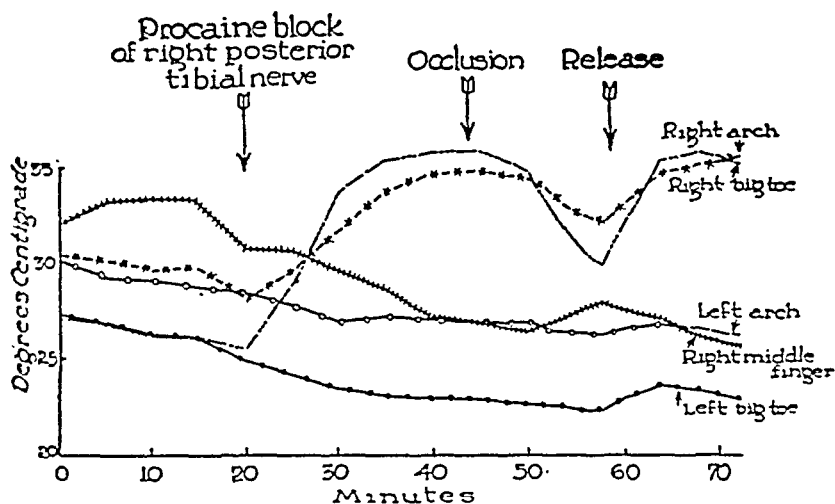


FIG. 17. Temperature observations of the combined effects of posterior tibial nerve block and the occlusion-reactive hyperemia test. Only the right posterior tibial nerve was blocked in each case. The occlusion-reactive hyperemia test was applied to both feet, not to the hands.

These curves represent the composite recordings of 10 psychoneurotic subjects.

factor added to the occlusion-reactive hyperemia test was the introduction of unilateral posterior tibial nerve block. A condensation graph of the results in 10 subjects was made in each series. The Class Ia trench foot cases closely paralleled the normal controls. (Figures 15, 16, 17 and 18). The reactions in the female showed no distinctive differences from those in the males except that it required from 10 to 15 minutes longer for them to reach thermal stability. The curves of the normal subjects and patients with psychoneurosis and trench foot showed close similarity. The curve for the right middle finger in the psychoneurotic showed a high initial temperature,

reaching maximum temperature of 33.4°C . during the first ten minutes in the constant temperature room but fell shortly afterwards to 30.7°C . This might be an expression of vasomotor instability. Apparently a very high degree of vasodilatation was obtained with blocks because the peak temperature reached after block was not exceeded by the combined effects of block and reactive hyperemia. The fact that the blocking of one extremity had very little influence over the other is also interesting and important, for then the unblocked extremity

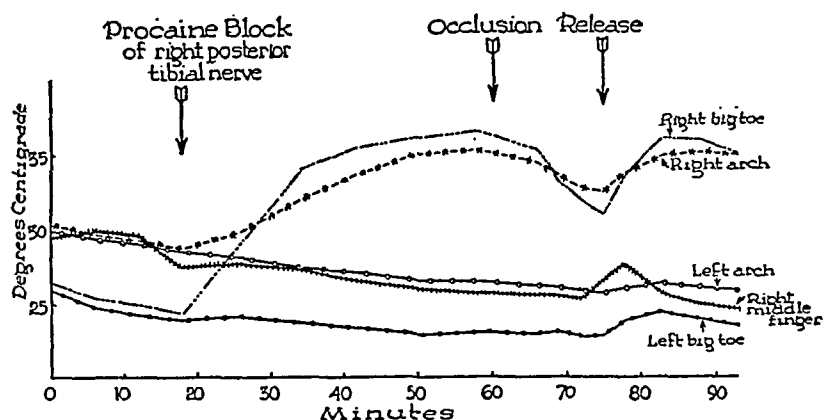


FIG. 18. Temperature observations of the combined effects of posterior tibia nerve block and the occlusion-reactive hyperemia test. Only the right posterior tibial nerve was blocked in each case. The occlusion-reactive hyperemia test was applied to both feet, not to the hands.

These curves represent the composite recordings of 10 Class Ia trench foot subjects.

served as a good control for the blocked one. The slight rise in the temperature of the finger simultaneously with the fall in temperature of the lower extremity was quite constant throughout these studies. There seemed to be an inverse ratio between the degree of fall in temperature of the part occluded and the degree of rise in temperature of the hand with its circulation intact. An adequate explanation for this phenomenon is still wanting. There was a distinct fall in temperature following occlusion in the foot with the nerve block. Simultaneously no fall following occlusion was noted in the foot without nerve block. The temperature before occlusion of 36.4°C . in the trench

foot patients in the right great toe with the nerve block, fell to 30.6°C . during occlusion of the circulation to the toe, whereas in the left big toe without nerve block the temperature was 23.0°C . at the onset of occlusion. The temperature fell only 0.5°C , that is, to 22.5°C . Apparently the higher the temperature at the beginning of occlusion and the more profound the vasodilatation, the greater the fall in temperature following occlusion, and the greater the rise during the phase of reactive hyperemia.

An interesting physiologic fact is here demonstrated. The total number of degrees rise following nerve block in the right great toe of the Class Ia trench foot was 12.2°C . This maximum was not exceeded in spite of the additional vasodilating influence of reactive hyperemia, indicating that the removal of neurogenic vasomotor tone had resulted in a maximum temperature rise in the right great toe. In the foot without nerve block the temperature rise in the great toe following release of occlusion was only 1.7°C . or only about one sixth the rise obtained in the foot with nerve block. Evidently reactive hyperemia of 15 minutes is not a very adequate method by which to obtain a high degree of vasodilatation and does not adequately demonstrate the full potentialities of the local circulation. The advantage, however, of reactive hyperemia as a test for disease in trench foot over vasodilatation produced by interruption of nervous impulses lies in the fact that this type of reaction occurs under integrating influences of the existing physiologic factors concerned with controlling the circulation of a part. A less artificial situation exists in the unblocked extremity. Therefore conditions regulating vessel caliber can be integrated in a fashion more closely resembling that existing in the normals when reactive hyperemia is employed without nerve block.

There is a similarity between the curves of normal males, females, psychoneurotics and Class Ia trench foot subjects. The tendency of the female subjects to take considerably longer than the males to reach stabilized temperatures warrants explanation. Motivated by modesty, these subjects refused to strip nude. They always wore their underclothing and frequently did not remove their khaki shirts. The importance of stripping the subjects nude has been stressed (*vide supra*). It is a known fact that coverings and warming of the

trunk will raise the temperature of the extremities, a phenomenon that most probably occurred in the female subjects and resulted in warmer hands and feet than in the male subjects.

4. *Patients with Miscellaneous Vascular Diseases*: Eight subjects with other types of abnormalities were subjected to the occlusion-reactive hyperemia test. They were: one with acute alcoholism, one with frostbite, one with uninjected varicose veins, five with severe (Class III) trench foot. The subjects with acute alcoholism and frostbite reacted in a fashion similar to the patients with Class Ib or Ic trench foot. The patient with varicose veins reacted in a normal fashion. The patients with Class III trench foot had no toes and in some instances had lost the distal portions of their metatarsals. With only two exceptions the terminal portions of the involved parts had infected draining ulcers. These lesions made it difficult to apply the thermocouples properly and, of course, toes could not be studied. The reactions noted for areas in the region of the distal ends of the metatarsals were difficult to interpret and compare with the reactions found in patients with intact feet because of the difference in tissue mass between the two groups and the presence of infected ulcers. As a matter of fact, the reactions found were similar to those described for Class Ia, Ib and Ic trench foot.

B. *Miscellaneous Quasi-objective Tests*

While performing the occlusion-reactive hyperemia tests, certain observations of a none too exact and objective nature were made. These extra observations required relatively little effort. Each is discussed below.

1. *So-called "state of vascular tone"*: Naide (8 and 9) claims that by measuring the temperature of the pad of the tip of the middle finger of a nude, fasting subject covered only with a cotton sheet and resting in bed in a room at 20°C. (68°F.) for 15 minutes he can determine the state of the subjects vascular tone. In order to apply Naide's observations in our study, his procedure was followed in nearly all of the normal and abnormal subjects studied.

The results of the test of Naide are summarized by Table 4 and Figure 19. Only 10.3 per cent of the normal male subjects and only 15.8 per cent of the females had temperatures below 25°C. Seven and

TABLE 4

Temperature of the Tip of the Right and Left Middle Finger at the End of 15 Minutes Rest in a Room at 20°C. (68°F.) of Patients with Mild Chronic Trench Foot and Control Subjects

	NORMALS				TRENCH FOOT						ALL GROUPS		PSYCHO-NEUROTIC		MISCELLANEOUS	
	Male		Female		1a		1b		1c		Right	Left	Right	Left	Right	Left
	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left						
Number of Subjects.....	39	16	19		28	17	6	6	7	7	41	30	53	41	9	1
Mean.....	30.39	29.37	29.09		29.63	30.53	30.38	31.63	31.34	30.78	30.45	30.92	30.81	30.60	28.14	23.6
Max.....	35.8	34.2	34.8		37.2	36.5	38.4	38	35.3	35.4	37.2	38	41.9	42.8	32.2	23.6
Min.....	22.5	22	22.2		22	23.8	1.1	22	22.8	24.2	21.1	22	21.8	21.2	24	23.6
Number with temp. below 25°C.....	6		3		8		8		2		18		18		3	
Number with temp. above 25°C.....	52		16		104		24		36		164		115		8	
% Below 25°C...	10.3		15.8		7.1		25.0		5.3		9.9		13.5		27.3	

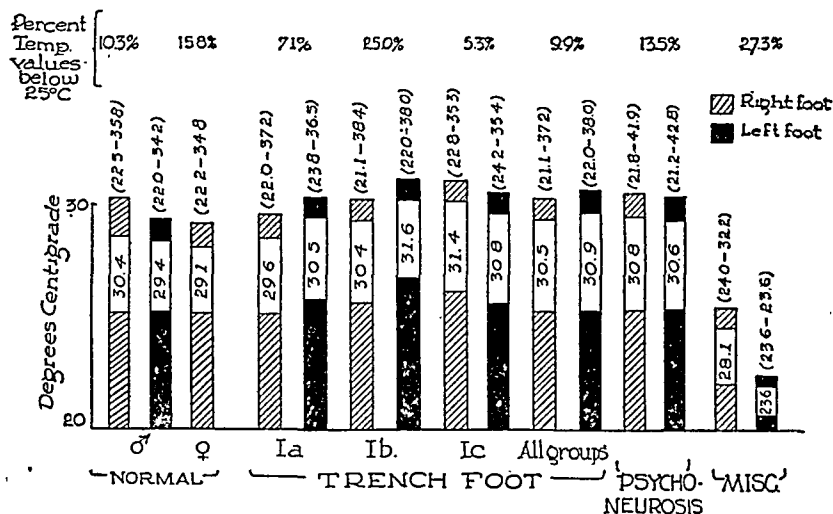


FIG. 19. This graph summarizes the observations of "Vascular Tone" (Naide^{8,9}), the temperatures being of the tip of the right and left middle fingers of the subjects at the end of 15 minutes' rest in a room temperature of 20°C. (68°F.). See text for details.

one tenths per cent of the patients with Class Ia trench foot, 25 per cent of the Class Ib, 5.3 per cent of Class Ic or 9.9 per cent of the total trench foot group had temperatures of the finger tip below 25°C. There were 13.5 per cent of the patients with psychoneurosis and 27.3 per cent of the miscellaneous group with temperatures below 25°C. Using Naide's criteria, it was found, therefore, that vascular tone among the trench foot patients was slightly less than that among the normal and psychoneurotic subjects and definitely less than found in the miscellaneous group of patients. In Naide's normal subjects over 50 per cent were found to be vasospastic, while in normal subjects in this study only slightly more than 10 per cent were found to be vasospastic. Since these studies were performed in New Orleans in the summer time, it is possible that climatic conditions may explain these differences. It is felt, however, that before Naide's test can be accepted for general use such variables as climate should be investigated. In any case, this test for vasomotor tone proved to be of little value in the study of patients with mild chronic trench foot.

2. *Skin Color*: Because of the variations in skin color in trench foot during various stages of the disease an attempt was made to quantitate the color phenomena noted during the three phases of the occlusion-reactive hyperemia test. Lewis' color charts (10) were employed for quantitating the colors in some of the normal and trench foot subjects. Near the end of Phase I, that is, just before occlusion of the circulation, and three minutes before the end of Phase II or near the end of the period of occlusion, the colors were estimated. Since there were marked variations in the nature of the skin color over various portions of the feet, only the color of the toes and dorsal areas of the feet near the toes was studied. These areas were chosen since they are frequently involved in trench foot. Color readings were therefore obtained for the subject resting horizontally in bed in a constant temperature room before his circulation was disturbed and another reading was obtained after 12 minutes of complete arrest of the circulation, before it had been released again.

The results are summarized by Tables 5, 6, 7, and 8. It can be seen from the Tables that the feet of the *normal subjects*, during the resting period, had a pale pink color with an occasional one showing a bluish hue to the background of color. After 12 minutes of complete arrest of

TABLE 5

Quasi Objective Observations on 13 Normal Subjects

The studies are concerned with measurements of the rate of refilling of pressure emptied skin vessels. The flush of reactive hyperemia, and variation in skin color measured by Lewis color chart.

SUBJECT	AGE	RATE OF REFILLING OF PRESSURE EMPTIED SKIN VESSELS (SECONDS)						FLUSH OF REACTIVE HYPEREMIA			Before occlusion	SKIN COLOR	
		At start of study		After 15 min. at 20°C.		At end of exper.		First pear- ap- ance max. flush	Degree				
		Rt.	Lt.	Rt.	Lt.	Rt.	Lt.		Rt.	Lt.			
													(sec- onds)
W.S.H.	26	3.8	3.0	6.0	6.0			4.3	45.2	3	+	i	(K blotches)
S.A.	25	3.0	2.8	4.0	3.5	8.0	7.0	9.5	57.2	2	+	K	(i blotches)
B.J.J.		3.0	3.0	5.0	5.0		7.4	8.8	57.3	1	+	K	(slight pink tint)
D.T.O.	24	8.5	8.5			14.0	15.5	9.0	38.0	2	+	K	(slight pink tint)
G.S.	23	5.0	5.0	10.0	11.5	19.0	20.0	10.8	60.4	2	+	j	
B.H.	25	4.0	4.0	6.0	5.8	6.0	5.0	45.0	3	+	+	K	(pink tint)
G.H.	23	3.8	3.5	5.2	5.0	12.8	10.2	5.0	32.2	3	+	K	(pink tint)
C.E.	23	5.0	5.0	10.2	10.0	15.0	14.8	15.0	58.0	1	+	K	(pink tint)
F.W.	22	2.2	2.0	2.5	2.5	6.0	9.8	8.8	47.6	1	+	K	(pink tint)
L.S.	23	4.5	4.5	7.5	8.0	8.0	10.0	12.0	56.0	2	+	K	
A.B.	23	2.0	3.0	4.0	3.5	13.0	13.5	9.0	62.2	1	+	K	(slight pink tint)
H.G.	24	3.0	3.0	6.0	5.0	8.2	10.5	7.0	53.0	2	+	i	(slight pink tint)
H.E.	23	10.0	8.0	11.0	10.5	11.0	10.2	9.0	61.0	3	+	+	
V.M.	25	6.0	6.5	15.8	13.0	15.0	14.4	12.8	49.6	1	+	j	(slight purple tint)
W.S.	26	4.0	4.0	5.4	8.0	8.0	9.0	9.0	49.0	3	+	K	(pink tint)
H.C.	23	5.0	5.0	5.0	7.0	7.0	11.0	50.0	1	+	+	j	(very slight pink tint)
F.F.J.	24	6.0	6.0	6.9	7.0	12.0	10.5	9.0	32.4	3	+	i	(pink tint)
H.R.	22	4.8	4.8	7.5	8.0	15.0	12.0	8.0	56.0	3	+	j	(pink tint)
Mean.....		4.6	4.5	6.9	9.1	11.1	11.2	9.1	50.6	2.1	+	1.7	+
Max.....		10.0	8.5	11.0	13.0	19.0	20.0	15.0	62.2	3	+	3	+
Min.....		2.0	2.0	2.5	2.5	5.8	6.0	4.3	32.2	1	+	1	+

TABLE 6
Quasi Objective Observations on 25 Class Ia Trench Foot Subjects

These studies are concerned with the same features as in Table 5.

SUBJECT	AGE	RATE OF REFILLING OF PRESSURE EMPTIED SKIN VESSELS (SECONDS)						FLUSH OF REACTIVE HYPEREMIA				SKIN COLOR		
		At start of study		After 15 min. at 20°C.		At end of exper.		Reactive Hyperemia App. of flush	App. of max. flush	Degree of flush			Before occlusion	12 min. after occlusion
		Rt.	Lt.	Rt.	Lt.	Rt.	Lt.			Rt.	Lt.			
T.R.	19	10.0	8.0	17.0	10.0			11.0	46.5	3	2	+	j (pink tint)	r-j (h blotches) l-j
K.B.	34	5.0	5.0	10.0	8.0			6.0	30.0	2	1	+	j	K (small j blotches)
L.L.	19	5.0	5.0	8.5	6.5			6.0	51.6	2	2	+	j (pink tint)	r-i-l-j
Mc.E.	30	7.5	7.5	9.0	9.0	5.5	9.0	7.0	55.0	4	3	+	j (pink tint)	i (j blotches)
C.C.	22	5.0	5.0	6.5	5.0	10.0	9.2	7.0	43.6	3	3	+	j (pink tint)	j (i tint)
J.H.	25	3.5	3.5	10.0	9.0	10.0	10.0	13.4	62.0	3	3	+	K (slight pink tint)	r-i-l-i
G.C.	23	5.0	5.0	8.0	11.0	19.0	17.0	12.5	62.0	3	3	+	j (pink tint)	i (j blotches)
W.W.	33	5.0	5.0	7.5	7.0	7.0	6.5	6.0	55.0	5	4	+	K (pink tint slight purple tint r big toe)	K (purple tint)
W.W.	33	5.5	5.5	8.0	8.0	8.5	9.0	9.0	53.0	3	3	+	K (pink tint)	j (purple tint)
J.H.	25	8.0	12.0	9.0	14.5	10.0	22.0	22.2	110.0	4	3	+	j (pink tint purple tint on r big toe only)	j (purple tint on big toes only)
J.H.	25	10.5	12.5	9.5	14.0	13.5	15.0	10.4	65.0	4	3	+	j (pink tint purple tint on r big toe)	j (purple tint K blotches)
M.E.	25	5.0	5.0	7.0	6.5	7.5	6.0	10.0	46.8	4	3	+	K (pink tint)	j (purple tint)
M.E.	25	4.5	4.5	8.0	7.5	10.0	9.0	10.5	44.6				K (pink tint)	j (purple tint)
L.J.	19	6.2	5.5	9.5	9.0	10.0	10.5	8.0	60.0	6	5	+	j (2 red tint)	j (h tint on both big toes)
H.C.	34	4.5	4.0	8.0	8.0	10.9	9.5	7.5	46.5	5	5	+	j (pink tint)	j (purple tint)
H.C.	34	8.0	6.0	8.0	11.0	10.0	12.0	11.0	55.0	2	2	+	K (slight pink tint)	j (slight purple tint)

H.C.	34	5.5	5.5	9.0	8.0	9.0	10.0	8.5	52.5	3	+	2	+	K (pink tint)	j
S.C.	19	8.5	8.0	15.0	15.0	15.0	15.0	8.8	76.8	3	+	2	+	K (purple tint on big toes only)	K (slight purple tint)
S.C.	19	4.0	6.0	5.5	6.5	12.0	19.0	14.0	60.0	2	+	2	+	K (mostly pink tint slight purple tint both big toes)	K (slight purple tint on big toes)
B.G.	21	5.0	5.0	7.0	6.0	9.0	10.0	10.0	60.0	4	+	3	+	j (reddish purple tint)	j (h blotches)
B.G.	21	4.0	4.0	4.0	4.0	6.0	6.0	11.0	56.0	4	+	3	+	j (pink tint)	r-g(j blotches) l-i (j blotches)
S.H.	20	10.0	10.0	19.0	18.0	16.0	18.0	13.0	127.0	4	+	3	+	K (g blotches on big toes only)	K (g blotches)
S.H.	20	9.0	9.0	16.0	18.0	15.0	18.0	15.0	68.5	4	+	3	+	K (slight purple tint)	j (slight purple tint K blotches)
C.J.	36	5.0	5.0	7.0	7.0	8.5	10.0	6.0	39.0	2	+	2	+	K (pink tint)	j (slight purple tint)
C.J.	36	4.0	4.0	7.0	7.0	9.0	10.0	8.0	52.8	2	+	1	+	K (pink tint)	K (slight purple tint on r big toe only)
Mean.....		6.1	6.2	9.3	9.3	10.5	11.8	10.1	59.2	3.4	+	2.8	+		
Max.....		10.5	12.5	19.0	18.0	19.0	22.0	22.2	127.0	6	+	5	+		
Min.....		3.5	3.5	4.0	4.0	5.5	6.0	6.0	30.0	2	+	1	+		

TABLE 7
Quasi Objective Observations on 7 Class Ib Trench Foot Subjects
 These studies are concerned with the same features as in Table 5.

SUBJECT	AGE	RATE OF REFILLING OF PRESSURE EMPTIED SKIN VESSELS (SECONDS)						FLUSH OF REACTIVE HYPEREMIA			SKIN COLOR			
		At start of study		After 15 min. at 20°C.		At end of exper.		Reactive Hyperemia	App. of max. flush	Degree of flush				
												Rt.	Lt.	
		Rt.	Lt.	Rt.	Lt.	Rt.	Lt.							
N.L. C.E. D.D.J.	34	2.5	3.5	3.2	5.0	5.4	6.5	5.0	45.2	6	4	+	K (pink tint)	j (h blotches)
	25	13.0	9.0	13.0	9.0	10.0	10.0	11.0	53.5	2	2	+	j (pink tint)	j (g tint)
	22	10.0	6.0	10.0	6.0			11.0	75.0	4	3	+	r-i (h blotches big toe) l-i (slight pink tint)	K (i blotches)
	25	5.0	5.0	7.0	6.5	7.0	7.0	8.0	41.4	4	4	+	j (pink tint)	i (purple blotches)
C.H. D.J. D.D.J. D.D.J.	22	5.0	4.0	5.0	4.5	8.6	5.0	8.4	51.0	5	4	+	K (pink tint)	K (purple tint, j blotches)
	22	3.0	3.5	8.0	8.0	11.0	9.0	9.0	60.0	3	2	+	j (pink tint)	j (H blotches)
	22	3.0	2.5	4.0	3.0	12.8	11.5	9.2	41.2	2	2	+	K (pink tint)	K (slight i tint)
	22	3.0	2.5	4.0	3.0	12.8	11.5	9.2	41.2	2	2	+	K (pink tint)	K (slight i tint)
Mean..... Max.....		5.9	4.8	7.2	6.0	9.1	8.2	8.8	52.5	3.7	3.0	+		
		13.0	9.0	13.0	9.0	10.0	11.5	11.0	75.0	6	4	+		
		2.5	2.5	3.2	3.0	5.4	6.0	5.0	40.0	2	2	+		

TABLE 8
Quasi Objective Observations on 4 Class 1c Trench Foot Subjects

These studies are concerned with the same features as in Table 5.

SUBJECT	AGE	RATE OF REFILLING OF PRESSURE EMPTYED SKIN VESSELS (SECONDS)						FLUSH OF REACTIVE HYPEREMIA			SKIN COLOR	
		At start of study		After 15 min. at 20°C.		At end of exper.		Reactive Hyperemia app. of flush	App. of max. flush	Degrees of flush		
										Rt.		Lt.
		Rt.	Lt.	Rt.	Lt.	Rt.	Lt.					Rt.
A.G.	29	4.0	4.0			4.0	4.0	6.2	53.6/4	+ 3	+	h (j blotches)
F.W.	19	2.0	1.5	2.0	2.0	4.0	3.0	7.0	36.2/3	+ 2	+	g (j blotches)
D.H.	22	4.0	4.0	6.0	7.0	7.0	6.8	6.8	70.0/4	+ 3	+	r-K (i blotches)
A.J.	34	6.0	5.0	8.0	6.0	7.0	7.0	6.0	67.5/3	+ 2	+	V (i blotches on big toes)
Mean.....		4.0	3.6	5.3	5.0	5.5	5.2	6.5	56.8/3.5	+ 2.5	+	
Max.....		6.0	5.0	8.0	7.0	7.0	7.0	7.0	70.0/4	+ 3	+	
Min.....		2.0	1.5	2.0	2.0	4.0	3.0	6.0	36.2/3	+ 2	+	

the circulation, the bluish background increased in intensity with the associated development of marked mottling (Bier's spots). Some of the blotches were almost purple in color, while others were white or apparently devoid of blood. The white blotches suggested islands of marked vasoconstriction. These areas of white blotches would often expand slowly centrifugally. The patients with *mild chronic trench foot*, Class Ia, tended to resemble the normal subjects except that there was, in many cases, decidedly more cyanosis, or blueness, to the background color both before and during occlusion of the circulation. The subjects with more advanced disease, Class Ic, showed much more evidence of cyanosis, even color values of *i* and *h* (10) were encountered before occlusion. Occasionally there was a reddish purple color to the background, a *V* color, for example. During the occlusion, the cyanotic color became much more intense than in the normal. The skin color findings in the moderately severe trench foot patients, Class Ib, were essentially in between that for the Class Ia and Ic patients.

In several instances, the deep purple which developed in the toes, usually in the areas where a previous mass of superficial tissue had undergone gangrenous changes, was very slowly displaced by the hyperemia following release of the circulation. It required, at times, as long as 180 seconds for the medical aspect of a big toe to become hyperemic or for the cyanosis to be completely displaced. In the normal subjects the flush of the reactive hyperemia reached the toes within 60 seconds, usually within 15 seconds, after release of the circulation.

3. *The Reactive Hyperemia*: During the occlusion-reactive hyperemia test, the reactive hyperemia or flush was studied in the toes in some of the normal and trench foot subjects to learn if there were any differences between the two groups of subjects: (1) in the time of onset in the toes; (2) in the length of time required for it to reach a maximum and (3) in the degree of flush developed. Since Lewis' color charts (10) did not lend themselves to an estimation of the degree of the flush, an arbitrary set of standards was established. The greatest degree of flush was considered a *six plus flush* and no flush as *zero flush*, thus making it possible to delineate seven grades of intensity of flush. The time of onset and time required for a maximum flush to be reached were measured in seconds from the moment of release of the circulation following the period of occlusion. Since it was impractical to estimate

these phenomena for both feet, only the toes of the right foot were observed. All of these measurements were performed by one person, who became quite proficient and trained in the estimations, and who was unaware of the interpretation of his findings.

These results are summarized by Tables 5, 6, 7, and 8. It can be seen that in general there was no significant difference in the time required for the flush to appear or for the maximum degree of flush to be reached. There was, however, a greater intensity of flushing in the patients with Classes Ib and Ic trench foot than in the normal subjects or the Class Ia trench foot patients.

4. *Rate of Refilling of Skin Vessels:* During the course of the occlusion-reactive hyperemia test, the length of time required for the vessels of the skin to refill once they had been emptied by pressure was estimated. This was done on the medial aspect of both toes, where superficial gangrene often develops in trench foot. These measurements were made in some of the normal and trench foot subjects. Pressure was applied firmly by grasping the medial aspects of the big toes with the thumb and the lateral aspects with the index and middle fingers. The pressure was maintained for about two seconds and then suddenly released, the time required for the blanched area fully to regain its color was measured in seconds. An effort was made to succeed with the measurements on the first attempt since the vessels were most probably altered locally by the pressure and ischemic effects, rendering succeeding measurements valueless. Such a measurement was made two minutes after entrance of the subject in the air conditioned room, again after 15 minutes in the room, and then at the conclusion of the occlusion-reactive hyperemia test just before the subject got out of bed to dress.

The results of these observations are shown in detail in Tables 5, 6, 7, and 8. The initial rate of refilling of the blanched skin vessels was greater in the normal subjects and those with Class Ic trench foot than in those with Classes Ia or Ib trench foot. However, as the subjects rested in the room at 20°C. (68°F.), the rate of filling of the blanched vessels of the skin decreased only slightly in the subjects with Class Ic trench foot, but decreased markedly in the normal subjects and in Class Ia trench foot patients. Those patients with Class Ib trench foot showed a decrease in the filling rate which was intermediate be-

tween that of the normal subjects and the Class Ic trench foot patients: There were essentially no differences in the refilling time in the right and left toes. These results indicate a much more labile blood supply in the normal subject, that is, a blood supply more adaptable to environmental cooling. The results, furthermore, indicate the fact that under the influence of cooling a greater amount of vasospasm occurred in the normal than in the Class Ic trench foot subject. For example, in the normal subject after 15 minutes of cooling the mean refilling time for both feet increased from 4.6 seconds to 8.0 seconds, an increase of 74 per cent. By the end of the experiment, the mean refilling time for both feet had reached 11.2 seconds, or an increase of 143 percent over the initial refilling time. In the Class Ic trench foot patients the mean initial refilling time for both feet was 4.1 seconds, and at the end of 15 minutes' stay in the cool room it had reached 5.3 seconds, an increase of only 29 percent. By the end of the experiments the refilling time had reached a mean of only 6.4 seconds or an increase of 56 percent over the initial mean.

This failure of the circulation of the foot of the trench foot patient to respond to environmental cooling, at least so far as the skin is concerned, may be an important factor in the subsequent sensitivity of these patients to extremes of environmental cold. The failure of trench foot to show a normal vasospastic response under the influence of the cool room may be evidence of nerve damage secondarily involving arteriolar function, rendering the nervous system less effective in pacing the arteriolar caliber to environmental needs. This failure is also concerned with local chemical vasodilating factors associated with inflammation.

C. Temperature of Various Parts of the Foot at Rest

During the course of the occlusion-reactive hyperemia test, the temperature of various parts of the feet was noted at the end of the first 15 minutes' rest in bed in the observation room. Preliminary and orientation studies suggested that there might be a difference in the resting temperature of the feet under constant room conditions. The results are summarized by Table 9, and Figures 20 and 21. It can be seen that the patients with chronic trench foot tend to have warmer feet in direct ratio with the severity of their disease than the normal subjects

or the patients with psychoneurosis. This is true not only for the foot as a whole but for the various individual portions of the feet studied (Figures 20 and 21 and Table 9). For example, the mean temperature for the four areas of the right foot of the patients with trench foot was $27.49 \pm 0.27^{\circ}\text{C}.$, for the same four areas on the left foot $26.87 \pm 0.24^{\circ}\text{C}.$, and for both feet together $27.18 \pm 0.18^{\circ}\text{C}.$ In the normal subjects, the mean temperature for the four areas of the right foot was $25.67 \pm 0.26^{\circ}\text{C}.$, for the left foot $25.03 \pm 0.08^{\circ}\text{C}.$, and for both feet $25.35 \pm 0.23^{\circ}\text{C}.$ Thus the feet of the trench foot patients tended to be about $2^{\circ}\text{C}.$ warmer than the feet of the normal subjects. The differences for each of the mean values for the normal subjects and the patients with trench foot were highly significant, with the probability of error varying from one in 31 to one in 6.5 million, depending upon whether or not a comparison is made between the warmest normal foot and the coldest trench foot temperature values (9). The mean values and statistical constants for the various areas of the feet are shown in the Table 9.

The mean temperature of the right big toe of the psychoneurotic patients was $25.2^{\circ}\text{C}.$; this is essentially $2.1^{\circ}\text{C}.$ lower than that of the trench foot patients. The temperature of the various areas of all the feet studied tended to follow that for the right big toe as a whole.

From these observations it became obvious that temperature levels greater than $27^{\circ}\text{C}.$ were more frequently encountered for various portions of the feet of patients with trench foot at the end of 15 minutes in bed in a room at $20^{\circ}\text{C}.$ than in a comparable group of normal subjects or patients with psychoneurosis. In the control subjects (normal male and female and psychoneurotic) there were relatively few temperature values above $27^{\circ}\text{C}.$ For example, when considering 136 temperature measurements for various portions of both feet of normal males only 22, or 16.2 per cent were greater than $27^{\circ}\text{C}.$, and none of these was greater than $29^{\circ}\text{C}.$ On the other hand, of 351 temperature measurements of both feet of the trench foot patients 161 values or 45.9 per cent were greater than $27^{\circ}\text{C}.$ Essentially the same relationships hold for the various portions of the feet when considered separately (Figures 20 and 21).

The more severe the chronic trench foot, the higher the temperature observed for the feet. For example, it was found that the mean tem-

TABLE 9

Statistical Constants for the Temperature in Degrees Centigrade for Various Portions of the Feet of Patients with Mild Chronic Trench Foot and Control Subjects

The temperature values were obtained at the end of 15 minutes rest in bed in a room at 20°C. (68°F.). See the text for details.

	MEAN	RANGE	STANDARD DEVIATION	COEFFICIENT OF VALUATION
Normal male soldier				
Right foot.....	25.67 ± .26	22.0-30.4	3.3 ± .2	12.9 ± .7
Left foot.....	25.03 ± .08	21.2-31.0	3.7 ± .2	14.8 ± .9
Both feet.....	25.35 ± .23	21.2-31.0	4.1 ± .2	16.2 ± .7
Rt. bunion area.....	27.28 ± .32	25.1-29.5	2.0 ± 0.2	7.3 ± 0.8
Rt. big toe tip.....	25.08 ± .41	22.7-29	2.6 ± .3	10.4 ± 1.2
Rt. 2nd toe tip.....	24.44 ± .37	22 -30.4	2.3 ± .3	9.4 ± 1.1
Rt. corn area.....	25.78 ± .38	23 -30	2.4 ± .3	9.3 ± 1.1
Lt. bunion area.....	26.64 ± .45	23 -29.9	3.6 ± .4	13.4 ± 1.5
Lt. big toe tip.....	24.39 ± .5	21.7-31	3.2 ± .4	13.1 ± 1.5
Lt. 2nd toe tip.....	23.72 ± .40	21.2-29.9	2.5 ± .3	10.5 ± 1.2
Lt. corn area.....	25.17 ± .43	22.8-21.2	2.7 ±	10.7 ± 1.2
Trench foot 1a				
Right foot.....	26.65 ± .29	22.2-34.2	4.4 ± .2	16.5 ± .8
Left foot.....	26.44 ± .27	22 -33	4.1 ± .2	15.5 ± .7
Both feet.....	27.06 ± .19	22 -34.2	4.2 ± .1	15.5 ± .5
Rt. bunion area.....	27.83 ± .51	24.2-30.8	3.9 ± .4	14.0 ± 1.3
Rt. big toe tip.....	26.26 ± .50	22.2-34.2	3.8 ± .4	14.5 ± 1.4
Rt. 2nd toe tip.....	25.76 ± .50	22.8-34.1	3.8 ± .4	14.8 ± 1.4
Rt. corn area.....	27.06 ± .33	23.3-30.7	2.5 ± .2	9.2 ± .9
Lt. bunion area.....	27.47 ± .30	23.6-30.8	2.3 ± .2	8.4 ± .8
Lt. big toe tip.....	26.11 ± .49	22 -31.8	3.7 ± .3	14.2 ± 1.3
Lt. 2nd toe tip.....	25.46 ± .45	22.8-33	3.4 ± .3	13.4 ± 1.3
Lt. corn area.....	26.50 ± .4	25.2-29.7	3.1 ± .3	11.7 ± 1.1
Trench foot 1b				
Right foot.....	27.63 ± .49	23.9-34.1	4.1 ± .3	14.8 ± 1.3
Left foot.....	25.31 ± .33	22.6-28.2	2.8 ± .2	11.1 ± .9
Both feet.....	26.48 ± .33	22.6-34.1	3.9 ± .02	14.7 ± .1
Rt. bunion area.....	28.8	24.8-29	2.37	8.23 ± 2.06
Rt. big toe tip.....	28.1	23.9-33	3.56	12.67 ± 3.17
Rt. 2nd toe tip.....	27.0	24 -33.4	3.42	12.67 ± 3.17
Rt. corn area.....	26.7	26.8-34.1	1.59	5.96 ± 1.49

TABLE 9—Continued
Trench foot 1b—Continued

	MEAN	RANGE	STANDARD DEVIATION	COEFFICIENT OF VALUATION
Lt. bunion area.....	26.5	24 -28	1.19	4.49 \pm 1.12
Lt. big toe tip.....	25.2	22.6-27.9	1.61	6.39 \pm 1.60
Lt. 2nd toe tip.....	24.3	22.9-28.2	1.62	6.67 \pm 1.67
Lt. corn area.....	25.4	25 -28.1	1.31	5.16 \pm 1.29

Trench foot 1c

Right foot.....	29.50 \pm .57	24.8-33.5	5.1 \pm .4	17.3 \pm 1.4
Left foot.....	29.47 \pm .58	24.8-35.4	5.1 \pm .4	17.3 \pm 1.4
Both feet.....	29.49 \pm .04	24.8-35.4	5.2 \pm .3	17.6 \pm 1.0
Rt. bunion area.....	29.8	24.8-32.2	2.29	7.68 \pm 1.81
Rt. big toe tip.....	29.9	24.9-31.4	3.19	10.67 \pm 2.52
Rt. 2nd toe tip.....	28.0	26 -33.5	2.85	10.18 \pm 2.40
Rt. corn area.....	30.0	26.3-32.9	2.23	7.43 \pm 1.75
Lt. bunion area.....	29.8	25.2-33.9	1.86	6.24 \pm 1.56
Lt. big toe tip.....	30.2	24.8-31.3	2.42	8.01 \pm 1.89
Lt. 2nd toe tip.....	27.6	24.8-35.4	2.09	7.57 \pm 1.78
Lt. corn area.....	30.0	26.6-32.2	3.03	10.10 \pm 2.38

Entire group of trench foot

Right foot.....	27.49 \pm .27	22.2-34.2	5.2 \pm .2	18.9 \pm .7
Left foot.....	26.87 \pm .24	22 -35.4	4.6 \pm .2	17.1 \pm .6
Both feet.....	27.18 \pm .18	22 -35.4	4.9 \pm .1	18.0 \pm .5
Rt. bunion area.....	28.43 \pm .49	24.2-32.2	4.8 \pm .4	16.9 \pm 1.26
Rt. big toe tip.....	27.43 \pm .51	22.2-34.2	5.0 \pm .4	18.2 \pm 1.4
Rt. 2nd toe tip.....	26.50 \pm .47	22.8-34.1	4.6 \pm .3	17.4 \pm 1.3
Rt. corn area.....	27.59 \pm .34	23.3-34.1	3.3 \pm .2	12.0 \pm .9
Lt. bunion area.....	27.76 \pm .25	23.6-33.9	2.4 \pm .2	8.6 \pm .6
Lt. big toe tip.....	26.75 \pm .45	22 -31.8	4.4 \pm .3	16.4 \pm 1.2
Lt. 2nd toe tip.....	25.77 \pm .36	22.8-35.4	3.5 \pm .3	13.6 \pm 1.0
Lt. corn area.....	27.05 \pm .41	25 -32.2	4.0 \pm .3	14.8 \pm 1.1

Psychoneurotic

Rt. big toe tip.....	25.3 \pm .4	21.8-31.0	4.0 \pm .3	15.8 \pm 1.2
Rt. 2nd toe tip.....	24.8 \pm .30	21.8-28.1	3.3 \pm .21	13.3 \pm 1.0
Both toes.....	25.33 \pm .23	21.8-35.9	3.3 \pm .2	13.1 \pm .7

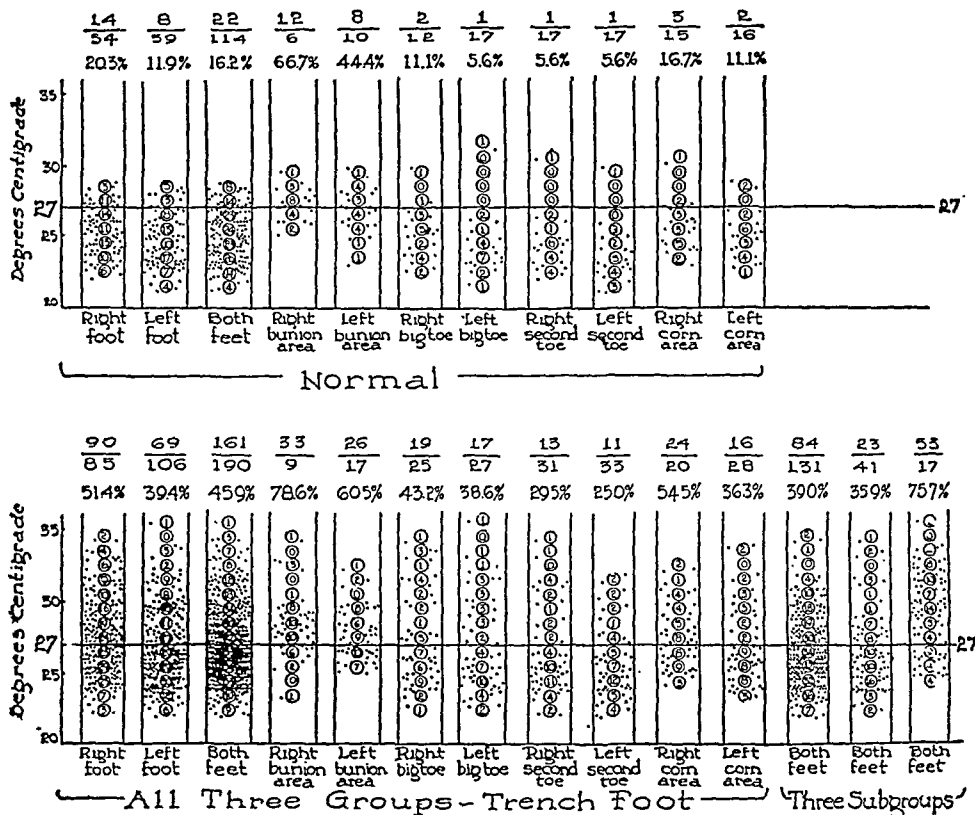


FIG. 20. A spot and summary graph of the temperature values of various areas of the feet of normal subjects and patients with trench foot after 15 minutes rest in bed in a room at 20°C. (68°F.). The temperature level of 27°C. (80.6°F.) was selected as a dividing line which tends to indicate a difference in the temperature of the parts in the two groups of subjects. The numerators of the fractions shown represent the number of temperature values above 27°C. and the denominator represents the number of values below 27°C. The percent values represent the per cent of the total temperature measurements which were above 27°C. In the lower graph, the three subgroups of trench foot represent from left to right, Classes Ia, Ib and Ic respectively.

perature of both feet was 26.5°C. in the patients with Class Ib chronic trench foot, while on the other hand the mean value was 29.4°C. for the

patients with Class Ic chronic trench foot. In the Class Ia chronic trench foot, of 215 temperature measurements of the feet, 84 or 39 per cent were greater than 27°C., while in the Class Ic chronic trench foot, 53 of 70 temperature measurements or 75.7 per cent were greater than 27°C.

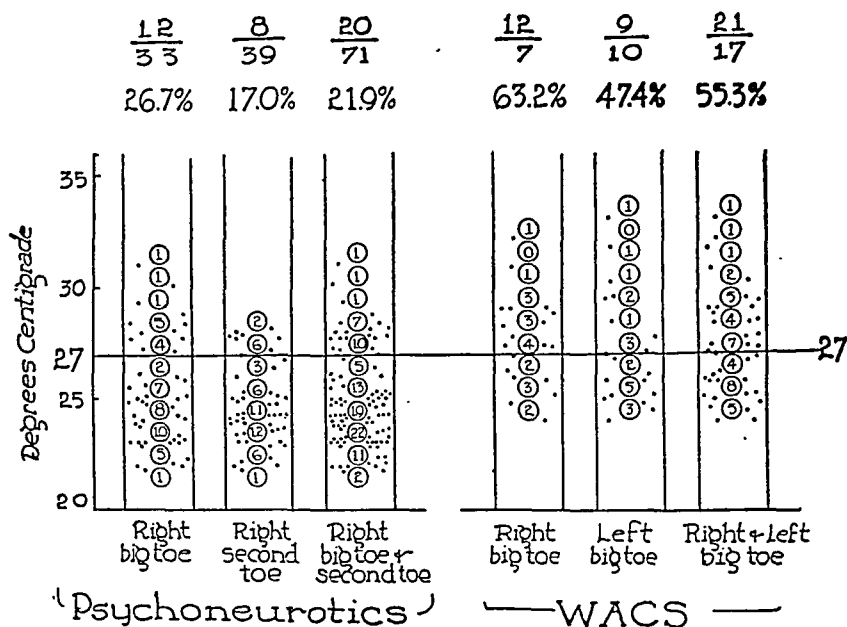


FIG. 21. A spot and summary graph of the temperature values of various parts of the feet of psychoneurotic patients and normal female subjects of the Women's Army Corps after 15 minutes rest in bed at a room temperature of 20°C. (68°F.). Twenty-seven degrees centigrade was selected as a dividing line with the fractions and percentage values as indicated in Figure 20.

It is understood that where gangrene is present, as is found in Class III trench foot, these observations may not necessarily apply. The values would depend upon the degree of gangrene and the site of application of the thermocouples. The temperature of the involved part would not reflect the temperature of the foot as a whole, since the very existence of gangrene demonstrates occlusion of the circulation.

D. *Rate of Water Loss Through the Skin and Sweating*

The rates of water loss through the skin of subjects with mild chronic trench foot (Classes Ia, Ib, Ic) and normal controls were studied simultaneously in a comfortable environment (temp. 20.3°C. (68.5°F.), 74 per cent mean relative humidity). Following these measurements under comfortable environmental conditions the room atmosphere was made hot and humid (mean temp. 48.7°C. (119.8°F.); mean relative humidity 53 per cent). Details of the environmental conditions are indicated in Tables 10 and 11. Since it was unnecessary, room conditions were not controlled too closely from experiment to experiment. The rates of water loss by sensible sweating were measured.

Methods used in these studies are those described elsewhere (11, 12). The measurements are direct and gravimetric. A normal and a trench foot subject rested in separate adjacent beds during these measurements, thus controlling in each experiment any variations in the environmental and other conditions. By such simultaneous measurements, although the conditions of the environments might vary somewhat from experiment to experiment, and by the mere fact that a normal and a trench foot subject were studied simultaneously under the same environmental conditions, any differences for the two groups of subjects (normals and trench foot) will be significant and adequately controlled. A five square centimeter area on the sole and dorsum of the right foot of 25 normal male subjects and 25 patients with trench foot was observed. The collections of sweat were made for 15 minute periods, three successive 15 minute collections being made for each environmental condition. The rates of water loss were expressed in milligrams per 10 square centimeters of skin area per 10 minutes.

The results are summarized in Tables 10 and 11 and Figure 22. The mean rate of water loss in the comfortable environment for the dorsum of the foot of the normal subjects was 5.6 mg. per 10 cm² skin area per 10 minutes (extremes 2.0 and 8.8) and the mean for the sole of the foot was 12.6 mg. per 10 cm² per 10 minutes (extremes 4.4 and 22.8). In the hot and humid environment the mean rate for the dorsum of the foot was 81.0 (extremes 33.6 and 151.2) and 33.8 (extremes 17.7 and 70.0) for the sole.

In the *patients with trench foot* the mean rate of water loss in the comfortable environment was 5.6 mg. per 10 cm² per 10 minutes (extremes

TABLE 10

The Rates of Water Loss in Comfortable and a Hot and Humid Environment from the Skin of the Dorsum and Sole of the Right Foot of 25 Normal Young Resting Adult Subjects

COMFORTABLE ENVIRONMENT					HOT AND HUMID ENVIRONMENT			
Subject	Rate of water loss mg./10 cm ² /10 min.	Room temperature		Relative humidity %	Rate of water loss mg./10 cm. ² /10 min.	Room temperature		Relative humidity %
		°F.	°C.			°F.	°C.	
Dorsum of foot								
W.H.	6.2	69	20.5	76	126.4	118	47.7	76
D.D.	6.4	68	20.0	80	54.0	124	51.1	48
F.N.	4.0	68	20.0	67	73.6	120	48.8	53
S.H.	6.6	68	20.0	76	48.0	118	47.7	51
T.C.D.	6.0	69	20.5	85	74.4	120	48.8	55
S.H.W.	3.6	68.5	20.3	83	63.2	124	51.1	52
L.S.	8.6	68	20.0	71	110.8	124	51.1	52
H.G.	8.0	68	20.0	80	77.6	119	48.3	55
G.W.	2.4	67.5	19.7	73.5	90.8	120	48.8	55
E.S.C.	8.8	68	20.0	80	135.2	115	46.1	80
C.R.	4.8	70	21.1	72	74.0	126	52.2	44
A.S.	3.4	68	20.0	64	151.2	118	47.7	64
P.D.	3.4	68.5	20.3	71.5	104.8	124	51.1	103
S.H.	2.0	68	20.0	71	73.2	122	50.0	46
L.B.	4.0	69.5	20.8	70	118.0	120	48.8	47
H.M.	8.0	67.5	19.7	78	64.0	116	46.6	57
V.G.	5.8	69	20.5	63	112.0	120	48.8	51
P.B.R., Dr.	6.8	69	20.5	72	77.2	122	50.0	52
L.S.	6.0	67.5	19.7	73	33.6	105	40.5	69
H.P.	7.8	69	20.5	76	84.4	120	48.8	53
W.K.	5.8	68.5	20.3	69.5	51.2	122	50.0	51
S.S.	6.0	67.5	19.7	69	34.0	120	48.8	49
F.N.	5.8	68	20.0	74	53.6	118	47.7	47
J.B.F., Dr.	6.0	68	20.0	76	96.4	122	50.0	52
J.C.	4.2	69	20.5	72	50.4	115	46.1	49.5
Mean.....	5.6	68.4	20.2	73.7	81.2	119.6	48.7	52.8
Max.....	8.8	70	21.1	85	151.2	126	52.1	100
Min.....	2.0	67.5	19.7	63	33.6	105	40.5	44
Sole of foot								
W.H.	12.2	69	20.5	76	29.6	118	47.7	76
D.D.	10.6	68	20.0	80	22.4	124	51.1	48
F.N.	5.2	68	20.0	67	25.2	120	48.8	53
S.H.	9.4	68	20.0	76	23.2	118	47.7	51

TABLE 10—Continued

COMFORTABLE ENVIRONMENT					HOT AND HUMID ENVIRONMENT				
Subject	Rate of water loss mg./10 cm. ² /10 min.	Room temperature		Relative humidity %	Rate of water loss mg./10 cm. ² /10 min.	Room temperature		Relative humidity %	
		°F.	°C.			°F.	°C.		
Sole of foot—Continued									
T.C.D.	7.6	69	20.5	85	29.6	120	48.8	55	
S.H.W.	17.0	68.5	20.3	83	28.0	124	51.1	52	
L.S.	10.8	68	20.0	71	25.6	124	51.1	52	
H.G.	13.2	68	20.0	80	28.0	119	48.3	58	
G.W.	8.2	67.5	19.7	73.6	26.8	120	48.8	55	
E.S.C.	16.2	68	20.0	80	56.4	115	46.1	80	
C.R.	7.4	70	21.1	72	26.4	126	52.2	44	
A.S.	6.2	68	20.0	64	42.0	118	47.7	64	
P.D.	7.8	68.5	20.3	71.5	70.0	124	51.1	103	
S.H.	4.4	68	20.0	71	24.8	122	50.0	46	
L.B.	7.6	69.5	20.8	70	26.8	120	48.8	47	
N.H.	22.8	67.5	19.7	78	47.6	116	46.6	57	
V.G.	13.2	69	20.5	63	65.2	120	48.8	51	
P.B.R., Dr.	10.2	69	20.5	72	36.8	122	50.0	52	
L.S.	10.6	67.5	19.7	73	41.2	105	40.5	69	
H.P.	7.0	69	20.5	76	17.6	120	48.8	51	
W.K.	9.0	68.5	20.3	69.5	50.8	122	50.0	53	
S.S.	9.4	67.5	19.7	69	22.0	120	48.8	49	
F.N.	7.2	68	20.0	74	27.6	118	47.7	47	
J.B.F., Dr.	10.4	68	20.0	76	24.8	122	50.0	52	
J.C.	7.8	69	20.5	72	26.4	115	46.1	49.5	
Mean.....	12.6	68.4	20.2	73.7	33.8	119.6	48.7	52.9	
Max.....	22.8	70	21.1	85	70.0	126	52.1	100	
Min.....	4.	67.5	19.7	63	17.7	1.05	40.5	44	

2.0 and 19.0) for the dorsum of the foot and 10.8 (extremes 3.4 and 21.2 for the sole. In the hot and humid environment, the mean rate for the dorsum of the foot was 86.1 (extremes 25.2 and 150.4) and 34.9 (extremes 20.0 and 74.4) for the sole. It was found, therefore, that the rates of sensible perspiration (mainly water of diffusion through the skin) (13) and sensible perspiration were essentially the same in the normal and chronic trench foot subjects (Figure 22).

In the comfortable environment the water loss was mainly by diffusion (13), and in the hot and humid environment the loss was mainly

TABLE 11

The Rates of Water Loss in a Comfortable and a Hot and Humid Environment from the Skin of the Dorsum and Sole of the Right Foot of 25 Resting Trench Foot Subjects of all Classes

COMFORTABLE ENVIRONMENT					HOT AND HUMID ENVIRONMENT			
Subject	Rate of water loss mg./10 cm. ² /10 min.	Room temperature		Relative humidity %	Rate of water loss mg./10 cm. ² /10 min.	Room temperature		Relative humidity %
		°F.	°C.			°F.	°C.	
Dorsum of foot								
F.W.	4.6	69	20.5	76	113.6	118	47.7	76
J.A.	7.2	68	20.0	80	70.8	124	51.1	48
W.W.	2.0	68	20.0	67	56.0	120	48.8	53
H.J.	7.0	68	20.0	76	100.0	118	47.7	51
W.H.	4.0	69	20.5	85	90.8	120	48.8	55
C.S.	19.0	68.5	20.3	83	98.0	124	51.1	52
J.C.	5.8	68	20.0	71	118.4	124	51.1	52
C.H.	7.8	68	20.0	80	81.2	119	48.3	55
J.D.	6.0	67.5	19.7	73.5	124.0	120	48.8	55
E.M.	8.8	68	20.0	80	150.4	115	46.1	80
S.H.	2.9	70	21.1	72	73.6	126	52.2	44
S.J.C.	2.4	68	20.0	64	91.2	118	47.7	64
C.G.	4.2	68.5	20.3	71.5	145.2	124	51.1	103
H.D.	3.2	68	20.0	71	70.0	122	50.0	46
E.C.	3.0	69.5	20.8	70	128.4	120	48.8	47
C.C.	10.4	67.5	19.7	78	80.8	116	46.6	57
W.F.	9.6	69	20.5	63	120.0	120	48.8	51
L.N.	3.2	69	20.5	72	71.6	122	50.0	52
H.J.	4.6	67.5	19.7	73	52.8	105	40.5	69
B.K.	6.0	69	20.5	76	67.6	120	48.8	53
J.D.	5.6	68.5	20.3	69.5	60.0	122	50.0	51
R.T.	2.6	67.5	19.7	69	51.2	120	48.8	49
L.L.	4.0	68	20.0	74	25.2	118	47.7	47
E.Mc.	4.8	68	20.0	76	76.0	122	50.0	52
G.A.	4.0	69	20.5	72	35.2	115	46.1	49.5
Mean.....	5.6	68.4	20.2	73.7	86.1	119.6	48.7	52.8
Max.....	19.0	70.0	21.1	85	150.4	126	52.2	103
Min.....	2.0	67.5	19.7	63	25.2	105	40.5	44
Sole of foot								
F.W.	19.8	69	20.5	76	35.2	118	47.7	76
J.A.	10.6	68	20.0	80	24.0	124	51.1	48
W.W.	5.0	68	20.0	67	24.0	120	48.8	53

TABLE 11—*Continued*

COMFORTABLE ENVIRONMENT					HOT AND HUMID ENVIRONMENT			
Subject	Rate of water loss mg./10 cm. ² /10 min.	Room temperature		Relative humidity %	Rate of water loss mg./10 cm. ² /10 min.	Room temperature		Relative humidity %
		°F.	°C.			°F.	°C.	
Sole of foot— <i>Continued</i>								
H.J.	12.0	68	20.0	76	24.4	118	47.7	51
W.H.	16.2	69	20.5	85	22.0	120	48.8	55
C.S.	21.2	68.5	20.3	83	24.8	124	51.1	52
J.C.	16.2	68	20.0	71	24.4	124	51.1	52
C.H.	11.2	68	20.0	80	32.4	119	48.3	58
J.D.	8.0	67.5	19.7	73.5	23.2	120	48.8	55
E.M.	10.0	68	20.0	80	98.8	115	46.1	80
H.S.	9.8	70	21.1	72	48.0	126	52.2	44
S.J.C.	8.2	68	20.0	64	48.4	118	47.7	64
C.G.	3.6	68.5	20.3	71.5	28.4	124	51.1	103
H.D.	3.4	68	20.0	71	28.8	122	50.0	46
E.C.	7.2	69.5	20.8	70	43.6	120	48.8	47
C.C.	14.0	67.5	19.7	78	30.4	116	46.6	57
W.F.	16.2	69	20.5	63	74.4	120	48.8	51
L.N.	8.8	69	20.5	72	39.6	122	50.0	52
H.J.	10.6	67.5	19.7	73	34.0	105	40.5	69
B.K.	6.0	69	20.5	76	26.0	120	48.8	53
J.D.	19.0	68.5	20.3	69.5	32.0	122	50.0	51
R.T.	7.8	67.5	19.7	69	20.4	120	48.8	49
L.L.	9.0	68	20.0	74	20.0	118	47.7	47
E.Mc.	8.0	68	20.0	76	40.0	122	50.0	52
G.A.	7.4	69	20.5	72	26.0	115	46.1	49.5
Mean.....	10.8	68.4	20.2	73.7	34.9	119.6	48.7	52.9
Max.....	21.2	70.0	21.1	85	74.4	126	52.1	103
Min.....	3.4	67.5	19.7	63	20.0	105	40.5	44

by sensible perspiration or the secretion of sweat by the sweat glands. Figure 22 shows that under the influence of a strong stimulus (of a hot and humid environment) to sweating, sweating from the soles is stimulated relatively little the rate of the water loss being only about three times greater than that in a comfortable environment. On the other hand, the rate of water loss from the dorsum of the foot increased about 14.5 times over that for the same area of skin in a comfortable environment. In the comfortable environment, however, the rate of

water loss was about twice as rapid from the skin of the sole as that from the skin of the dorsum of the foot.

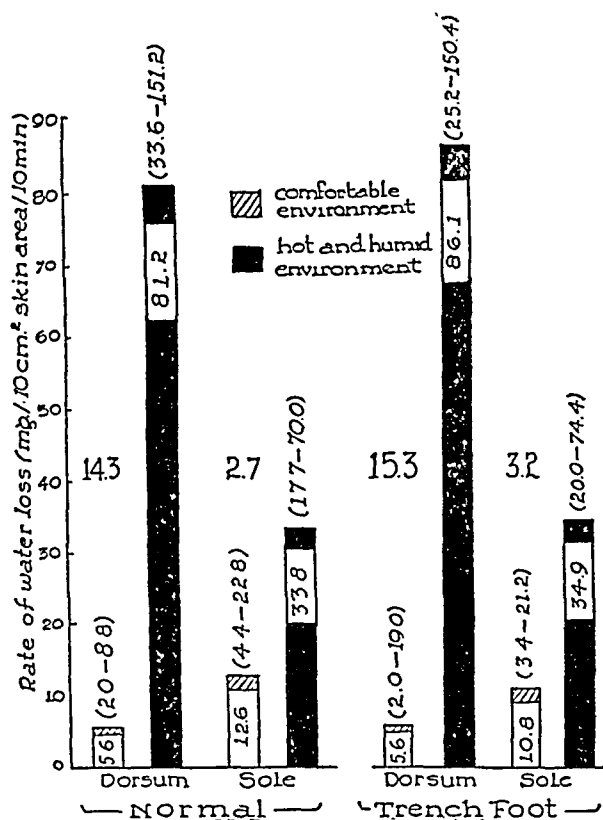


FIG. 22. The rates of water loss through the skin of Class I trench foot patients and normal control subjects compared for a comfortable environment (mean temperature 20.3°C. (68.5°F.), mean humidity 74%) and a hot, humid environment (mean temperature 48.7°C. (119.8°F.), mean humidity 53%). An area of 5 square centimeters was selected for study on the sole and dorsum of the feet.

The values 14.3, 2.7, 15.3 and 3.2 represent the number of times the rates of water loss increased in the hot and humid environment over that in the comfortable environment.

Since the number of sweat glands in the sole of the foot is essentially 2.5 times the number per unit area on the dorsum and the rate of sweat water loss on the dorsum of the foot is essentially 2.5 times that on the

sole in the hot and humid environment, the individual sweat gland on the dorsum of the foot produced sweat at a rate over six times that of an individual gland of the sole when the environment was hot and humid.

The finding of equal rates of sweating for the normal and trench foot subjects both in the comfortable and hot and humid environments certainly indicates a normal functional state of the sweat glands in these mild chronic trench foot patients. This was true for all three grades of mild chronic trench foot, indicating that the functional repair of at least the superficial dermal structures had occurred even in Class Ic. Popoff (7) has found that the anatomic restoration of sweat glands occurs relatively early.

IV. GENERAL DISCUSSION

All considerations relevant to the above data must be influenced by the prime consideration that this discussion is limited to mild chronic trench foot. A period of at least five to nine months has elapsed between the most recent exposure to the etiologic factors concerned with trench foot and these studies. Severe cases were not studied. Although many of the findings may very well apply in either more acute or more severe forms of the disease than are dealt with in this paper, since they have not been tested here, it is unsound to base any predictions on them.

The fact that these studies were conducted in summer in New Orleans, where the weather is warm and humid, may have influenced these data. Naide (8, 9) had devised a test for vascular tone in man with criteria which do not apparently hold true in these studies. Perhaps the fact that his work was done in Philadelphia while this work was done in New Orleans may be the source of differences. Subjects acclimatized to warm humid weather may manifest differences in circulation from those subjected to a colder, drier climate in spite of the fact that both groups may be under identical conditions of temperature and humidity in the control room during the actual observations.

A group of subjects were tested on a basal fasting routine and also from two to three hours after meals. No difference was demonstrated in these groups, as far as skin temperature is concerned; hence there is no need to interrupt the regular meal schedule. The only essential

factor is that at least two hours must elapse between the most recent meal and the test.

An important consideration is the accurate ($\pm 0.25^{\circ}\text{C}.$) control of temperature in the constant temperature room. The skin thermocouples are influenced by environmental temperature *per se* as well as the temperature of the subjects' skin. Variations in environmental temperature will therefore influence the temperature readings and provide an important source of error. Since one is interested in variations in skin temperature only, the room temperature must be kept constant. Humidity control need not be as accurate as temperature control. A range of from 50 to 65 per cent is permissible. Humidity above or below these critical levels will produce either delayed or accelerated surface evaporation, and thus interfere with temperature control. This humidity range is not difficult to attain and quite comfortable for the patient.

The duration of the subject's stay in the control room must be accurately measured and controlled. Evaluation of skin color, disappearance and return of skin color on pressure, and so on, (Tables 5, 6, 7, and 8) are greatly influenced by the duration of time the subject has spent in the control room. Since duration of exposure and environmental temperature have considerable influence upon the caliber of skin vessels, careful regulation of temperature and duration of exposure are essential to proper evaluation of vascular and thermal phenomena.

Judging skin color is a rather inaccurate procedure. For that reason, all skin color studies are considered as "quasi-objective." There are considerable individual variations among the observers. Skin color is frequently patchy rather than uniform, thus rendering it difficult to decide which areas of skin represent the significant color changes.

The disappearance and return of skin color on pressure may also be classes as a "quasi-objective" test. Accurate timing of the phenomenon is difficult. Nevertheless, observations in the resting extremity two minutes after entering the control room, 15 minutes later and then at the end of the experiment disclosed interesting facts (Tables 5, 6, 7, 8). The Class Ic trench foot patients have demonstrated the existence of dilated skin vessels with a failure to adapt to environmental

cooling by manifesting a consistently more rapid "refilling time" throughout the study. The Class Ib patients showed a "refilling time" intermediate between normal and Class Ic. Apparently the local circulatory responses of the subpapillary venous plexus, capillary bed as well as the arterioles, are inhibited in their reaction to environmental cooling in Class Ic trench foot. In moderate atmospheric conditions, such as prevail in the control room, this is a subclinical phenomenon uncovered only by careful testing. Under more extreme atmospheric conditions the failure of the superficial vessels to keep pace with environmental needs may be at least a factor in the abnormal sensitivity which trench foot patients manifest to extremes of heat or cold. At earlier or more acute stages of the disease the rates of refilling of pressure emptied skin vessels are probably quite different from those in the mild chronic trench foot.

The studies of sweating have disclosed a complete regeneration of the sweat gland function in this group of mild chronic trench foot. These measurements have been of no value in differentiating normal from trench foot subjects or quantitating the degree of trench foot in this group. Nevertheless, since there is an early return of this type of skin appendage to normal after superficial tissue destruction, the measurement of sweat may be used as an early sign of functional regeneration of superficial tissue. The so-called "perspiratory personality" (14) and the numerous clinical references to the presence of excessive sweating as a manifestation of vasomotor instability in trench foot have not been supported in these studies of mild chronic trench foot. The interesting physiologic difference of the functional qualities of the sweat glands of the sole and of the dorsum of the foot discovered in these studies has been indicated above.

In the introductory remarks the premise that chronic mild trench foot patients are probably suffering from a form of inflammation, which is produced by physical agents, was discussed. Descriptions of chronic inflammation already available in the literature in support of this concept have already been mentioned. The results of the observations described above serve to confirm this premise. For example, the initial temperature (Table 3, Figures 1 through 9) of the foot in the trench foot patient was higher in general than a homologous part in the normal subject. The more severe the clinical picture, the higher

was the initial pedal temperature. Such findings are compatible with the presence of inflammatory reaction manifested by superficial vasodilatation. In addition, it was noted in the occlusion-reactive hyperemia test that the degree of reactive hyperemia, as evidenced by the degree of rise in temperatures from the reactive hyperemia effect, was more pronounced in trench foot than in the normal subject. The degree of change was directly proportional to the clinical severity of the case, that is, Class Ic showed greater change than Class Ib and Class Ib greater than Class Ia. There were only slight differences noted among Class Ia trench foot, normal and psychoneurotic subjects. Lewis (6) has shown that the degree of reactive hyperemia developed in a part following occlusion is directly related to the rate of metabolism and oxygen consumption. Inflammation accelerated the rate of tissue metabolism and oxygen consumption; therefore, all things being equal, during the period of occlusion a greater oxygen debt and hyperemia would be expected in the presence of inflammation as compared with normal tissue.

The relatively rapid refilling time of the blood vessels of the skin in the trench foot patient supports the existence of vasodilatation which could be inflammatory. The fact, however, that the period of stay in an atmosphere of 20°C. (68°F.) failed to bring about a normal degree of vasoconstriction of the skin vessels is further support of the existence of inflammatory vasodilatation.

The clinical observations in these patients, as well as observations by others made on clinical and histologic studies, support the premise of chronic inflammation (2). Since demonstrable chronic inflammation may exist in mild chronic trench foot, a test demonstrating the presence or absence of continued activity of chronic trench foot should entail, in part, at least, the accumulation of data in support of the existence or non-existence of inflammation. Since very mild chronic trench foot subjects with activity and former trench foot patients who have returned to normal are being studied, the evidence of inflammation will *a priori*, be slight and subtle. Therefore, a test outlined below is designed to uncover or rule out, in part, at least, low grade inflammation.

Obviously, exact criteria cannot be set up on the basis of only 46 trench foot subjects. Due to unavoidable circumstances, the number

was limited. Adequate control studies were done, so that a foundation has been established to delineate the range of normal variations. Eighty-nine normal male, 51 psychoneurotic male, and 19 normal female subjects were studied, many of the subjects, normal and trench foot, being subjected to repeated observations. Thirteen miscellaneous patients with mild peripheral vascular disease were also examined. A total of 218 individual subjects were studied.

The evaluation of other forms of peripheral vascular disease for comparison purposes by these tests did not fall within the scope of this paper. Nevertheless, the control subjects in future studies should include many varieties of disease states. Such groups tend to orientate the test in relation to the normal and the abnormal. Abnormal controls would establish the specificity, if any, of this procedure in the field of peripheral vascular disease. It is known that the occlusive vascular diseases produce an extremity of reduced rather than elevated temperature. Where major peripheral vessels are occluded, local inflammation cannot initiate hyperemia easily because the functioning vascular channels are not adequate to supply the part with blood. The finding of increased temperature in an extremity and the demonstration of potentialities for a marked increase in that temperature would confirm the presence of relatively adequate vascular channels to the skin. The uniformly great increase in temperature after posterior tibial nerve block indicates in the cases of mild chronic trench foot at least that there is no great lack of potential vascular channels in this condition. The presence of adequate vascular channels does not, however, insure an efficient blood supply since these channels must be so controlled and integrated that they can pace themselves to the needs of the part. A test to determine the adequacy of circulation to a part must, therefore, establish not only the presence of adequate vascular channels but also the ability of these channels to react appropriately to the demands of the tissues of the part tested.

The results of the observations described above indicate very strongly that with certain simple, objective, correlated procedures it might be possible to show that a mild chronic trench foot has not returned to normal even though ordinary clinical studies show no abnormalities. Like the electrocardiogram in heart disease, the finding of normal reactions to the test outlined below cannot be considered defi-

nately to rule out subtle or latent trench foot. It may, with further study, be safe to conclude otherwise. Furthermore, it is well to note at this time that the tests outlined in detail below show definite promise, but it would certainly be unsafe to generalize about their application at present, for many variables may modify chronic trench foot. Furthermore, the series, though observed repeatedly, was relatively small, a fact supported in part by statistical analyses (Table 3). It is also quite possible that the clinical evaluation in some of these patients may be in error. Criteria set upon the basis of clinical classification may be inaccurate. The subdivision of the mild chronic trench foot patients into classes Ia, Ib and Ic may certainly raise the question as to whether such a comparatively detailed subdivision can be made. Certain subjects considered as Class Ib might certainly be in Class Ia or vice versa, or patients listed in Class Ic might be in Ib or vice versa. There is little likelihood, however, that a Class Ic patient would be mistaken for a Ia patient or vice versa. The simplicity of the procedures and the definite nature of the findings, however, make it highly worthwhile to extend the observations to include many more patients with trench foot and control subjects, both normals and patients with many disease states. Such variables as climate, duration of the disease, occupation, age, exercise, shoes, type of clothing, and other factors should be checked. The tests outlined below are not complicated and can be applied to many subjects by technicians of usual training. Nevertheless, it is necessary to consider all details outlined seriously, for thermocouple determinations require special care in their use, even though they are simple to employ.

A. Tests for Mild Chronic Active Trench Foot

1. *Room conditions* must be uniformly controlled throughout to ensure a temperature of 20°C. (68°F.), with variations not to exceed $\pm 0.25^\circ\text{C}$. ($\pm 0.9^\circ\text{F}$). The relative humidity may vary from 50 to 65 per cent. The rate of movement of the air in the room near the subject should not exceed 15 feet per second and should be uniform.

2. *Preparation of subject:* The subject requires no special preparations. He should not eat or smoke within three hours of the observations. and, of course, should be free from any complicating illnesses. He should rest comfortably in bed, nude, covered over the trunk from

the upper third of the thighs to the shoulders with an ordinary cotton sheet. A blood pressure cuff of six inch width (15 cm.) with about a six foot length cloth is wrapped snugly, but not tightly, around the lower third of the thighs just above the knee. These cuffs, guarded by valves, are connected to a constant pressure tank of air automatically regulated to 280 mm. of mercury pressure. A thermocouple is placed on the pad of the tip of each big toe, if possible (more parts may be observed but this is not necessary. The application of the cuffs and thermocouples should not require over 90 seconds. The temperature of these two parts is measured continuously, preferably by an automatic pen recording galvanometer, until the test has been completed.

3. *Fifteen minute temperature of the parts:* The temperature of the part is noted at the end of the first 15 minute period of stay in the room.

4. *Rate of refilling of pressure emptied vessels of the skin:* The toe is squeezed firmly for about 12 seconds between the thumb and index and middle fingers by placing the thumb on the medial side of the subject's big toe and the two fingers on the lateral aspect. The pressure is suddenly released, and the time required for the emptied skin vessels to refill is measured by a stopwatch. "Refilling time" is measured at the end of two minutes' stay in the room, at the end of 15 minutes' stay, and again at the end of the entire study just before the subject gets out of bed to dress.

5. *Occlusion-reactive hyperemia test:* After the temperature of the parts has reached a stabilized baseline, that is, maximum difference in two successive temperature measurements of $0.2^{\circ}\text{C}.$, the pressure in the blood pressure cuffs around the thighs is suddenly raised to 280 mm. mercury by opening valves connecting the lumina of the cuffs to the pressure tanks. At the end of 15 minutes of occlusion of the arterial and venous circulations the pressure in the cuffs is suddenly released by opening and closing proper valves. The temperature of the parts is measured continuously during the entire period.

B. Interpretations

Under the conditions in which these studies were conducted the following interpretations seem justified but require further evaluation and study:

(1). If the temperature of the part at the end of 15 minutes' stay in the room is above $29^{\circ}\text{C}.$ there is almost 100 per cent chance that the

toe of the subject is not normal. If it is above 27°C . there is about a 75 per cent chance that the toe is not normal.

(2). At the end of two minutes and 15 minutes' stay in the observation room the rate of refilling of the pressure emptied skin vessels showed no significant difference between the trench foot and control subjects. If at the end of the entire study the rate of refilling is less than 8.0 seconds, the chances are almost 100 per cent that the part is not normal.

(3). In the occlusion-reactive hyperemia test, if the temperature of the big toe falls more than 5°C . during the period of occlusion and shows a maximum rise of 5 or more degrees centigrade during the period of reactive hyperemia, the chances are about 100 per cent that the part is still diseased. If the fall during the period of circulatory arrest is 3.6°C . and the rise during the period of reactive hyperemia is 4.4°C ., the chances are about 90 per cent that the part is not normal. If the fall is greater than 3°C . and the rise after release of the circulation is greater than 3°C ., the chances are about 75 per cent that the foot is abnormal. In fact, with a fall of 2°C . during the occlusion and a rise of 2°C . during release the patient has over a 50 per cent chance of being abnormal.

(4). When all three above phenomena are definitely abnormal in reaction, the chances of the part being diseased approach 100 per cent and are more definite than if one of these reactions were suggestively abnormal. The availability of two separate objective phenomena and one quasi objective phenomenon leads to greater accuracy. The accuracy is further ensured by observing a part on both sides simultaneously, one part being a control over the other.

V. SUMMARY AND CONCLUSIONS

The purpose of this study has been to find an objective test which will aid the clinician in determining whether or not patients who formerly had acute trench foot are still showing evidences of active disease. In trench foot patients with extensive tissue damage and tissue loss, pathology is apparent. Patients with subjective complaints lacking obvious objective disease present a difficult problem to evaluate precisely.

The premises (1) that trench foot is an inflammatory disease produced by exposure to cold and moisture and (2) that tissue reaction

and repair persist long after initial exposure have been important bases in this study. It was decided to investigate the value of temperature changes in the involved part as a major criterion for the existence and degree of inflammation. Temperature studies by means of skin thermocouples, supplemented by quasi objective evaluations of skin color and the rate of refilling of pressure emptied skin vessels, were used to uncover and quantitate local inflammation and the functional rate of the basal circulation. The comparative rates of water loss from the skin of normal and trench foot subjects were also observed. There was no remarkable difference in sweating between normal and trench foot subjects, whether in a comfortable or a hot and humid environment.

During the course of this study certain facts have become apparent. The initial temperatures of the foot of the mild chronic trench foot subject was higher than that of the normal or psychoneurotic subject, and there was a direct correlation between the clinical severity of the disease and the height of this temperature. Class Ia patients, who border on normalcy, showed very little difference, if any, from normals. Classes Ic and Ib patients showed a distinct difference from normal. Trench foot cases also showed a fall in temperature after the circulation to the foot was occluded and a reactive hyperemia rise after release of the circulation which were much greater than the normal but proportionate to the severity of the disease; Class Ic manifests the most extreme effects; Class Ia resembled normal most closely, and Class Ib fell about intermediately between Ia and Ic. Since the findings showed only minimal differences between the Class Ia trench foot and the normal, there may be overlapping. The methods used were quantitative while the clinical evaluations of the trench foot could not have been equally precise.

Trench foot subjects did not adapt to environmental cooling like the normal or psychoneurotic controls. This fact was demonstrated by studies conducted on the refilling time of pressure emptied skin vessels. The Class Ia subjects showed little difference from the normals. Class Ib showed a distinct difference, and the Class Ic patients manifested little tendency to adjust to environmental cooling at 20°C. (68°F.)

An index, which might be appropriately called the "Activity Index," based upon the features of initial stabilization temperature, number of

degrees temperature fall following 15 minutes of occlusion, and rise during hyperemia after release of the circulation can be devised to express the amount of inflammatory activity in a part injured by cold and moisture. Such an index might be further supported by data on the refilling time of pressure emptied skin vessels. It is not feasible at this time to base such a critical evaluation upon a comparatively small number of cases. An index which could numerically express activity and for which definite quantitative values can be stated to correspond with the degree of activity would simplify the handling of large numbers of subjects. The improvisation of such an index is quite possible. Certainly, further study over a larger group of trench foot subjects is warranted to find it. However, a group of observations have been outlined which seem to have promise as tests for activity in mild chronic trench foot. Based upon these limited studies, possible interpretations have also been indicated.

Acknowledgements. We wish to express our appreciation of the efficient and important technical assistance given by Mr. G. Morgavi and Sgt. Vivian Littell (W. A. C.). Misses Elsie Landry and Shirley Wiederecht assisted in the analysis of the data.

BIBLIOGRAPHY

1. DARLAND, W. A. N.: The American Illustrated Medical Dictionary 18th edition. W. B. Saunders, Co., 1938.
2. FRIEDMAN, N. B.: The Pathology of Trench Foot. *Am. J. Physiol.*, 21: 387, 1945.
3. KARSNER, H. T.: Human Pathology. J. B. Lippincott Co., 1942.
4. KAUFMANN, MAX: Pathology for Students and Practitioners. Blakiston, Philadelphia. 3: 2081-2085, 1929.
5. Bull. U. S. Army Med. Dept. 4: 265, 1945.
6. LEWIS, T.: The Blood Vessels of the Human Skin and their Response. Shaw and Sons, London, 1927.
7. POPOFF, N. W.: The Digital Vascular System. *Arch. Path.*, 18: 295-330, 1934.
8. NAIDE, M.: A Test for Vascular Tone in Humans and its Application to the Study of Vascular Diseases with Special Reference to the Etiology and Prevention of Thrombophlebitis. *Am. J. Med. Sc.*, 207: 606, 1944.
9. NAIDE, M., AND SAIJAN, A.: The Primary Influence of Basal Vascular Tone on the Development of Postocclusive Collateral Circulation and in Selecting Patients for Sympathectomy. *Am. J. Med. Sc.*, 209: 478, 1945.
10. LEWIS, T.: Standard Colours for the Use in the Study of Vascular Reactions of the Human Skin. *Heart*, 15: 1, 1929-31.

11. NEUMANN, C., COHN, A. E., AND BURCH, G. E.: A Quantitative Method for the Measurement of the Rate of Water Loss from Small Areas with Results for Finger Tips, Toe Tip and Postero-superior Portion of the Pinna of Normal Resting Adults. *Am. J. Physiol.*, **132**: 748-756, 1941.
12. BURCH, G. E., AND SODEMAN, W. A.: Regional Relationship of Rate of Water Loss in Normal Adults in a Subtropical Climate. *The Am. J. Physiol.*, **138**: 603-609, 1943.
13. BURCH, G. E., AND WINSOR, T.: Rate of Insensible Perspiration (Diffusion of Water) Locally Through Living and Through Dead Human Skin. *Arch. Int. Med.*, **74**: 437-444, 1944.
14. OSBORNE, J. W., AND COWEN, J.: Psychiatric Factors in Peripheral Vasoneuropathy after Chilling. *Lancet*, **249**: 204-206, 1945.

The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Tulane University School of Medicine.

THE USE OF THE PSYCHOSOMATIC CONCEPT IN MEDICINE

FELIX DEUTSCH, M.D.

The topic you have chosen to be discussed by me as the second lecture in the memory of Miss Brogden is very near to my heart, since, for the past twenty-eight years, much of my research I devoted to this subject. For this reason, I consider it not presumptuous to accept the honor of delivering the address to you today.

A discussion of the psychosomatic concept presupposes a clarification of what this concept means, how it developed, and how it moved so much into the center of our interests. Firstly, it must be stated that the concept is an old one, was renewed thirty years ago, and is today under scrutiny again. The old idea of the demons which enter the body and make it sick has been certainly abandoned, but not yet as completely as we would like to be the case; it has changed for some time to the idea of the magic power—rooted so deeply in the infantile idea of omnipotence—the magic power which remains to a great extent the nucleus of psychotherapy based on the concept of the exertion of mutual influence, between human beings. The demonic idea became replaced by the concept of hypnosis, suggestion and autosuggestion. For a long time this concept dominated the mind and body problem as far as research and therapy was concerned. Time and again, hypnotic experiments were conducted, repeated and duplicated up until today, to prove how emotional factors can influence physiological processes. Much coal was carried to Newcastle.

It would have led us into a blind alley if Freud's concept of the unconscious had not given the research a new impulse. He himself began his investigation with hypnotic therapy, until he discovered that not the conscious conflicts make somebody sick, but the forgotten, repressed, unresolved, unconscious conflicts lead to bodily changes, under given conditions. The first analytical research in this field is connected with the names of Ferenczi, Groddeck and Jellife. Having been Freud's physician at the time of the onset of and during his tragic disease, he influenced me to begin this research from the psychophysiological point of view. Then some twenty-five years ago, I (1)

used the term "psychosomatic" with the idea that this research aims, as I wrote at the time, to study the personality structure through the observation of the bodily behavior. I proposed as the goal of the therapy, to loosen the psychosomatic fusions, to clean, so to speak, the organ systems from the old psychic entanglement, and to free them from the unconscious, pathological, instinctual influences, in order to safeguard the biological functions.

As Freud's ideas paved the way for psychosomatic research from the psychoanalytical point of view, Cannon's (2) discoveries of the emergency functions of the organism as danger signals and safety devices for the equilibrium of the organism, brought light into this field from the physiological side. The concept of the unconscious on the one hand, and the fact-findings of the autonomic functions under emotional stress on the other hand, put the psychosomatic concept on a sound basis. Both of these principles, the physiological and the psychological one, are indispensable for an understanding of the psychosomatic concept of today. From another alley of research came welcome support for the consolidation of this concept. The animal experiments of Pavlov and his concept of the conditioned reflexes, and the more recent experiments of Lidell, Gant, Richter, Masserman and others brought convincing facts, which drew the attention of the medical men to the psychosomatic concept.

In surveying the opinions of present-day psychosomatic concept, we meet here very controversial view points. When the first issue of the *Journal of Psychosomatic Medicine* appeared, the editors wrote an editorial in which the opinion was ventured that by and large, "the whole medicine is psychosomatic, since psychic and somatic phenomena take place in the same biological system and are probably two aspects of the same process". Hence, psychosomatic medicine is rather an approach to medicine as applied to all aspects of medicine and surgery. "When the integration of psychiatry into general medicine is completed, we will no longer need the term psychosomatic because good medicine will be psychosomatic". Weiss (3). Several authors see in the name a dualism which does violence to nature because mind and body are one. It is argued that every disease is psychosomatic, for no somatic disease is entirely free from psychic influences. Fenichel (4) Binger (5). For this reason, it is proposed that the clumsy term

psychosomatic medicine would be better substituted by "The New Empiricism" or "Bio-medicine". Lewin (6). Furthermore, it would be better to have the term reserved for this category of functional disturbance, which is physical in nature and consists of physiological changes, caused by the inappropriate use of the function in question. An example would be peptic ulcer, which may be considered as the physical result of an inappropriate use of the stomach by emotional factors. "The ulcer is the incidental physiological consequence of a psychogenic attitude". This concept is not joined by others who claim that stomach symptoms of a gastric neurosis, secretory and motor, are not a substitute expression of an emotion, but its physiological counterpart, or its physiological corollary, and the peptic ulcer in itself, has nothing whatever directly to do with any emotion". Alexander (7). Another proposal comes from a well known author, Kubie (8), who wants to abandon the ominous term psychosomatic and proposes to replace it by the "all-inclusive term somatization", used now in military psychiatry, Menninger (9), as the name of any process by which a partial discharge of psychological tension occurs through the psychosomatic representation, either of the emotion itself, or of the external relationship involved, or of the conflict out of which the tension arises, or finally of the instinctive functions which give rise to the conflict. In the application of this term to the different psychosomatic disturbances, Kubie distinguishes first between external somatization, involving the external structure of the body; second, internal somatization, involving the internal organs; third, instinctual somatization, involving the apertures of the body; and fourth, diffuse somatization, involving the entire body.

In rejecting this term, another author, Masserman (10), hopes that the medical people will divest themselves of the defensive body around dualism implicit in the term psychosomatic. He expresses this opinion in the statement that our science may accept this new branch as what it is: "a study of the personal behavior of physiologically integrated human beings, interacting with the personal and social milieu, as each conceives and interprets it in terms of his own abilities and experiences". With this orientation, he thinks there need be "no bridges nor hyphen among biology, medicine and psychology, since there are no artificial boundaries to bridge". An authority in this field, Stanley Cobb (11) writes

that "psychosomatic" is by its etymology a liaison field between neurology, psychiatry and medicine. It seems to him to be a clinical field that takes up the study of the *abnormal* functions set going by emotional stimulation in any system of the body except the nervous system, and as the study of the lesions caused by such abnormal functioning. In short, simply that field of clinical medicine where the internist can help the psychiatrist and where the psychiatrist can help the internist in the study and treatment of disease.

Another leading psychiatrist, Nolan Lewis (12) finds also the term not a particularly fortunate one, but he goes further saying that psychosomatic medicine is not a speciality: "*It is not a branch of medicine*", rather a concept or a method of approach to the problem of etiology, pathology, diagnosis, and therapy, wherever they are found in the general medical and surgical specialties. However, he concedes that in any attempt to evaluate a patient psychosomatically, a methodological study is necessary; first, of the personality; second, of his method of adapting to life's situations; third, of those details of the family history, that may have a bearing on the problem; fourth, of the manner in which the illness develops; fifth, of the possible immediate precipitating factors; and sixth, of the nature of the physical rigor or rigors upsetting the situation for possible emotional conflict. It should further be investigated whether the symptom is utilized in an attempt to solve some emotional conflict, and whether the pattern has been used before early in life. Last but not least, Dunbar (13) calls it a *branch of medicine* which is concerned with an appraisal of both the emotional and the physical mechanism involved in the disease of the individual patient with particular emphasis on the influence that these two factors exert on each other and on the individual as a whole. "Psychic and somatic represent two angles of observation from which the organismal unit should be studied".

It seems to me that we should not be too much concerned with whether this kind of methodological study of a patient is called a branch of medicine or not. By and large, as we see, many authors think that the term psychosomatic is only a convenience until a better term is found. If we bring the different opinions under one hat, we might say: *Psychosomatic medicine is the systematized knowledge of how to study bodily processes which are fused and amalgamated with emotional processes of the past and the present.*

It is clear that the psychosomatic concept of today takes it for granted that any organic function, not only the pathological one, can be interpreted from the psychological point of view. In applying Woodger's concept of the universe stated in his "Biological Principles" (14), to the psychosomatic concept, we will see of what one must be aware when he uses this concept in medicine. Woodger adopts "the general picture of the universe as a series of levels of organization and complexities, each level having unique properties of structure and behavior, which, though depending on the properties of the constituent element, appear only when these are combined into the higher whole. The phenomena of a higher level cannot be understood without the knowledge of the behavior of its constituents at the lower level".

In these words we find partly the answer to the question of why it took so long before the psychosomatic concept could gain ground in medicine. The phenomena of the higher level—that is, the psychosomatic behavior—were for a long time not understood because a connection of the higher level with the constituents of the lower level could not be seen. That leads us to the question of how to examine a patient to find these connections.

Various methods have been employed to obtain the right information about psychosomatic disorders from the psychological point of view. I remind you of Whitehorn's (15) writings on interviewing. All of them tend to get an understanding of the patient's social, vocational, family (early and present), sexual adjustment including physiological and psychological behavior. The first method which I should like to call "the double track method" is the commonest. The clinical examination is made by one examiner, the psychiatric examination by another. The findings so obtained are then evaluated for their possible interrelations. It is easy to see that such construction would at times become arbitrary guesswork, and will often not correspond to the facts.

The second method is to search out in the patient's life all the possible emotional experiences that might be assumed to have a traumatic effect on the patient. Then one seeks to determine whether the onset of the organic symptom coincided with a psychic trauma. It takes note of all the organic events in the patient's life as well as of all his emotional experiences. The more coincident the traumatic

emotional experiences with the organic disturbances, the more convincing are the *correlations*.

A third method is "the biographical method". Weiszaecker (16). This concept is that all illnesses are not precipitated by chance, but are motivated by intense emotional events in the individual's life. An understanding of the various phases of the organic illness depends on the ability to uncover the genesis of the emotional events concomitant with the illness. One has not to elicit the phenomena in chronological order if one has the concept that the illness is not the onset but the result of many coinciding factors. The assumption is that the only possible way to validate the principle of psychosomatic unity is to introduce the personality into the total pathology. According to this concept, some organic illnesses begin just at the turning point of biographical crises. These crises do not occur suddenly but are an integral part of the course of the individual's life. The patient's biography inextricably interweaves somatic, emotional and mental components linked to a personality. However, the biographical method does not explain the symptoms. It merely records a kind of naive observation of the behavior and the psychic reactions of the patient. It aims at finding in the life of a patient as many *catastrophes* as possible that may form an emotional background of the organic illness. Since the examiner must interpret the material of the history to correlate psychic and somatic symptoms, there is always the danger that the results will be inconclusive. Only when the patient himself is able to give the somatic and psychic interrelations as plausibly connected will the psychosomatic unity be unquestioned.

For this reason, another method called "Associative Anamnesis", Deutsch (17) has been developed which records not only what the patient says but also how he gives information. It is of consequence not only that the patient tells his complaints but also in what phase of the interview, and in which connection he introduces his ideas, complaints, and recollection of his organic and emotional disturbances. From this point of view, obtaining the material and writing the case history cannot follow the well established pattern of the ordinary medical case history. In psychosomatic diseases, we are not so much interested in obtaining as many facts as possible, as in getting information that has not been prepared for the occasion. If one properly elicits

this kind of history-taking, one learns how the symptoms developed and what the symptoms meant to the patient from early childhood. The patient is stimulated to give the information needed, when asked to describe his organic complaints, without being aware of the psychological background of his illness. He will give the material necessary for a proof of the psychosomatic unit in his illness only if he is not aware of what it reveals to us about his emotional life. If the examiner allows him to talk without being asked leading questions, the patient will usually give a detailed account of his complaint and ideas about his illness. When he has exhausted his ideas and recollections about his organic disturbances, he will stop and wait to be asked a question. The examiner waits until it is clear that the patient will not continue spontaneously. Then he repeats one of the points of the patient's last sentence in an interrogative form. Usually the examiner repeats one of the organic complaints, the last mentioned, being careful to use the same words as the patient. The patient then usually gives new information centering around his symptoms and is stimulated to further associations. He drifts into giving a communication in which he inattentively mixes emotional and somatic material.

In this type of interview, we learn a great deal about the old and the recent conflicts of the patient, how they were and are motivating his life, and how the patient reacts to people with whom he is and was living. We get hints about the family relationships of early life, clues as to how, why and when the symptoms developed, how the psychic make-up was thereby influenced, how the organic disturbances were utilized in conflict situations, and finally the rôle of the afflicted organ functions in the psychosomatic pattern.

Any psychosomatic examination is done in order to prove that the already premorbid personality used in its development certain parts of the body and bodily functions for the expression and *solution* of emotional conflicts which become later symptoms of the organic condition. It should show that the subjective bodily sensations are simultaneously symptoms of the neurosis and of the organic disease. That implies that it should be proved that the subjective symptoms of the disease follow the pattern laid down in the bodily and personality make-up. On the whole, the interview will show the fundamental, dynamic, uninterrupted interrelation of the patient with its inner and outer

environment, and, as it was pointed out before, how the phenomena of a higher level are linked up with the constituents of the lower level. From this point of view, the term "*psychogenic*" which was first so fruitful for, but later seriously blocking the application of the psychosomatic concept in medicine, becomes outmoded. There does not exist the alternative of "psychogenic or not psychogenic." The fundamental question is what is the interrelationship of certain psychological factors with certain biological ones. To make it clear: not co-existence, nor corollary, or correlation, nor parallelism of psychological factors but *interrelationship* of these factors is what we will find. More specifically, the interview should elicit the roots of the *interaction* of the emotional life and the bodily function in question, *what* led to the choice of the organic system for the expression of the conflict, and furthermore, what factors of the environment, past and present, contributed to the establishment of the psychosomatic symptom complex.

But there remain in those interviews other problems to be answered; that is, whether the patient went, in his early life, through common emotional conflicts with their concomitant organic responses, or whether the conflicts met from the beginning a less resistant organic constitution which then paved the way for the later disease and for a personality disorder. That raises the question of how far those personality disorders contribute to the deterioration of bodily functions and whether those personality disorders are specific for certain psychosomatic entities.

At present, one part of research in psychosomatic medicine goes in the direction to prove that certain specific psychosomatic disorders occur in individuals with a specific psychological constellation. Another part of research, as Whitehorn stated some years ago, appears to be in the direction of close psychological scrutiny during periods of physiological change. If the research in this direction can be carried through convincingly, it may give the answer to the X which is so puzzling in many psychosomatic entities, particularly in allergy. Let us take asthma as an example; one of the leading allergists, Rackemann (17), put it this way: "Asthma from other causes besides allergy may come from "asthmatic state" which indicates a reaction pattern which is characteristic. Let it be called X". Then he writes, "Why stop to consider an X for asthma and allergy, when another philosopher might

suggest a Y for arthritis and a Z for mucous colitis. For each person, the reaction pattern appears to be uniform and fairly constant. Is there any characteristic of the early disease which would throw light on the ultimate prognosis? Who has the X"? he asks, and continues, "What is needed is a further study of depletion including nervous exhaustion due to stress and strain to find the mechanism by which these psychosomatic disturbances will produce their symptoms. Obviously, a complicated and difficult problem. It will take many statistical studies to make sure about these things". Being consistent, Rackemann put then amongst the requirements necessary for the development of allergic symptoms, the X., i.e., "the asthmatic state", ahead of all other requirements, and let the capacity to develop sensitiveness, i.e., allergy, and the capacity to produce and to react to histamine substances, follow. Those statements show what remarkable change towards psychosomatic concepts has taken place in medicine.

Before we try to give tentatively the answers to the X, Y, and Z which Rackemann mentions, it has to be emphasized that the problem of personality specificity in certain psychosomatic entities is still incompletely solved, and some authors are skeptical about the attempt to relate definite psychosomatic pictures to definite personality structures.

As far as *asthma* is concerned, it has been suggested that the early affections of the respiratory tract, as whooping cough or frequent colds, plus its use for the expression of conflicting tendencies throughout the childhood create a personality of a specific structure with compulsive trends. Deutsch (17). The mothers in these cases are usually efficient, domineering figures who encourage the dependency, and at the same time, suppress the aggressive tendencies. Hence the conflicts underlying this interaction between the mother and child form the background for asthma. The fathers of those patients are usually passive, kind, and less efficient personalities. The asthmatic attacks tend to be precipitated by situations, conscious and unconscious ones, that stimulate those aggressive tendencies or threaten to separate the patient from the mother figure, more in the sense of the danger of an estrangement from her, due to some tabooed temptations,

to which the patient is exposed. Hence, the asthmatic seizure is an anxiety equivalent due to the fruitless attempt to eliminate a forbidden content through the respiratory tract.

The Y of Rackemann has also found some reasonable explanation. The personalities of patients with *rheumatoid arthritis* betray very often that they have a great need for motility to overcome anxiety, that they could act out and suppress their expression of hostility in the muscular apparatus, that they take the pain as a personal offense which they resent and feel as a kind of punishment against which they protest. They overcome very often aggressive impulses directed against some person, through an identification with this person. They underestimate very often the limitations of activity demanded by the somatic impairment. It is remarkable how some chronic deformative arthritis cases screen their impairment in their behavior and talk about the future although hopelessly crippled.

The specific emotional constellation of *mucous colitis*, the Z mentioned before, may be discussed at best in connection with other gastro-intestinal disorders.

The important personality trends in the *gastric neuroses* cases are intense unconscious wishes which the patient cannot admit to himself. It is thought that the stomach symptoms are conditioned by the tendencies which serve as chronic psychic stimuli to the stomach function. In other words, many patients who have a strong, unconscious need for affection, a strong desire to be appreciated and taken care of, psychologically translate these trends as the need to be fed. At the same time, they cannot admit these impulses to themselves, and as a consequence, overcompensate with a demonstration of great energy and great endeavor. They are afraid to be dependent or ineffectual. Nevertheless, their strong unconscious tendencies to be dependent cause reactions in the gastro-intestinal tract so that the stomach tries to serve a double function. It tries to serve the function of emotional reception of love as well as acting as the organ of digestion. This is too difficult for the stomach to accomplish because the need to be taken care of (fed emotionally) is acting as an unusual or foreign and constant stimulus. This stimulus is responsible for overactivity and excessive secretion beyond the digestive needs. Moreover, this "need to be fed and loved" trend is being opposed by a stronger need to reject the un-

acceptable idea of dependency and ineffectuality, and this conflict may result in stomach symptoms.

A patient with *stomach ulcers* appears outwardly to be a very active, efficient person, but proves actually to be a hungry, dependent person, whose unsatisfied cravings for love he is unable to accept. When his ambition is thwarted, or his efforts towards success and accomplishment and superiority are too strained, he will have a tendency to run for cover, to slip back into a dependent child-like attitude, and surrenders. These passive, receptive cravings, when not satisfied, and when continually repressed, actually find their expression in a primitive way. The craving for love and care, when unsatisfied, can be felt as if it were a need for food, to which the body then reacts with a kind of chronic hunger. Such a state keeps the stomach in continuous preparedness for food which it does not receive. Its muscular wall contracts, resulting in gnawing sensations and hunger pains; its mucous membrane becomes engorged with blood, and its acid-secreting glands are over-stimulated. Wolff (19).

The trend of *colitis* cases are often quite different from the peptic ulcer patients. They unconsciously feel that they have the right to take and demand, for they 'always give sufficiently'. They feel often guilty and depressed and cross, and show grief, if they cannot give something in return for what they received. This "something" they give is usually the childish substitute of bowel movements for real values, sometimes given to express their love or aggression. Sometimes there is overtidiness, overcleanliness, hoarding the foremost personality pattern.

The characteristic traits of the personality of *hypertension* appear to be an excessive need for a secure, dependent relationship, which they are unable to find or to accept. They have a weak, submissive attitude in which fear of injury, emotional isolation and suppression of hostility are prominent features. In addition there seems to be tendency to experience frustration in relationships with other people, both social and sexual.

The experience is that the chronic hypertension cases belong to the groups of overly inhibited, sensitive, yet, at the same time, intensely hostile and aggressive individuals who try to cover up their hostility.

The hypertension develops when circumscribed neurotic symptoms which serve for the draining of pent-up hostile impulses are absent.

In the main there exists a conflict between passive, dependent, feminine tendencies and overcompensatory, competitive, aggressive, hostile impulses which lead to fear and increase the flight towards the passive attitude. The patient cannot accept the passive attitude nor express his hostile impulses.

It is a question of to which degree the high blood pressure itself accounts for the characteristic personality.

Not only psychosomatic disorders but also true organic diseases were investigated concerning their personality pattern. To give only one very brief example, it was found that the psychological background of *diabetes* is in some cases the feeling of deprivation with an increase of passive personality tendencies. These passive personality trends can find their expression in many ways, depending of course, on the pre-morbid personality. It seems as if the reactive depression in these cases is due to the food deprivations, but the depressive factors are based on experiences of loss of love in the pre-diabetic life period, and is therefore a depression of a primary nature. Daniels (20).

In completing a discussion of the use of the psychosomatic concept in medicine, it seems to be appropriate to discuss briefly the *psychotherapeutic* use of this concept. It presupposes that the therapist becomes firstly, thoroughly acquainted with the medical and psychic tools of therapy; secondly, that he is well trained in how, when and which of these tools to use in the special case. Of course, for practical purposes, it might not be necessary to become specialized in this therapy. In medical practice, it often happens that the physician prescribes a drug, the effect of which he is not in the least aware, but which doesn't prevent that it might be a great help to the patient. The same is true in psychotherapy where so many do not know which healing device they have used when their patients claim that they feel better. "Sometimes a sudden and dramatic faith cure, may, by the very fact of its occurrence, considerably alter one's status". Whitehorn. However, the physician's surprise about his therapeutic success yields often to a belief in his magic power, and lets him make up sometimes a theory afterwards which should justify the use of his power in relation to the patient; but it is a truism that human beings want to

be cured by magic, and therefore often willingly surrender to this approach.

The *methodological* treatment of psychosomatic disorders on the other hand has a certain goal. It aims to dissociate, to free the afflicted organs from their unconscious meaning, from their symbolizations, from their abuse for defenses against anxiety, from the inhibitions as well as from their use for substitutional gratifications. When that has been achieved, we must realize, beyond that, nothing more can be done by psychotherapy to reconstitute the functions. However, sometimes it may be necessary to draw another organic function into an emotional setting through treatment, in order to free the diseased organs from a less desirable involvement. By and large, the treatment always aims to strengthen the personality and to enable the ego to give up the abuse of a function and to change its "body politic". In this way, even the perception of unpleasant and painful sensations, based on organic tissue changes, can be relieved.

What has to be borne in mind is that a patient will not give up his symptom, and therefore a psychosomatic disorder cannot cease, as long as the emotional setting is not reshuffled and the psychic economy rearranged and psychic energies redistributed. The disappearance of the symptoms proves that such a process has happened. It has further to be realized that in the course of the therapeutic process, the gradual disappearance of the organic expression of the psychological imbalance will be accompanied by the appearance of a transient psychic expression of this imbalance until the equilibrium is regained. That is due to the fact that the ego is still ill at ease in giving up the protective use of the body against danger from within. The emotional symptoms which a patient then shows can be either anxiety itself or a compensation of anxiety expressed in a denial of such feeling and in exaggerated self-confidence.

It is an axiom that the patient will resist any change of his choice of conflict solution as long as he feels not assured of a better solution or as long as the conflict is not solved. Therefore, the assurance of the patient by the physician that nothing is wrong with him organically can only rarely help him. What he needs, as I said, is a better conflict solution which he can accept.

In medical psychotherapy of psychosomatic disorders, we have to take into account that the treatment of the involved organic system

by drugs has to be gradually abandoned. It is incompatible with the therapeutic concept to continue the treatment of an organic function with drugs when the patient's interest in this part of the body should be dissolved. To reach the therapeutic goal, it might very often not suffice to treat the inner emotional setting alone. Then *sociotherapy* has to go hand in hand with psychotherapy. That means the environmental setting has to be handled and managed too. That is done at best by the trained social worker. The smooth function of this teamwork, sociotherapy and psychotherapy, depends on the intelligent co-operation of the two factors, doctor and social worker.

BIBLIOGRAPHY

1. DEUTSCH, F. Der gesunde und der Kranke Koerper in Psychoanalytischer Betrachtung. Intern. Ztsch. f. Psychoanalyse 12: 3, 1926.
 2. CANNON, W. B. The Wisdom of the Body. New York. Norton 1932.
 3. WEISS, E. Modern Attitude in Psychiatry. Columbia University Press, 1946.
 4. FENICHEL, O. Nature and Classification of the so-called Psychosomatic Phenomena. Psychoanal. Quarterly 14: 3, 1945.
 5. BINGER, C. The Doctor's Job. W. W. Norton & Co. New York. 1945.
 6. LEWIN, B. Review of Binger's "The Doctor's Job". Psychosom. Med. 8: 4, 1946.
 7. ALEXANDER, F. Fundamental Concepts of Psychosomatic Research. Psychosom. Med. V. 5: 3, 1943.
 8. KUBIE, L. Annals N. A. of Sciences. Vol. XLV Art. 6., p. 607.
 9. MENNINGER, W. The Annals Amer. Acad. Politic. and Social Science 3: 39, 1945.
 10. MASSERMAN, J. H. Principles of Dynamic Psychiatry, W. B. Saunders Co. Philadelphia, 1946.
 11. COBB, S. Borderlands of Psychiatry. Harvard University Press. Cambridge, Mass. 1943.
 12. LEWIS, N. Psychosomatic Medicine. Univ. of Pennsylvania Bicentennial Conference. Univ. Pennsylvania Press. 1941.
 13. DUNBAR, H. Emotions and Bodily Changes. Ed. 2. New York. Columbia University Press. 1938.
 - id. Psychosomatic Diagnosis. Paul B. Hockes. New York. 1945.
 14. WOODGER, T. H. Biological Principles. Kegan Paul, London. 1929.
 15. WHITEHORN, J. C. Guide to Interviewing and Clinical Personality Study. Arch. Neurol. and Psychiatr. 52: 197-216.
- WHITEHORN, J. C. Psychotherapy. Modern Medical Therapy in General Practice I. Williams & Wilkins Co. Baltimore. 1940.

16. WEISZAECKER, V. Studien zur Pathogenese. George Thieme. Leipzig, 1935.
17. DEUTSCH, F. The Choice of Organ in Organneurosis. Intern. f. Psychoanal. 20: 252, 1939.
DEUTSCH, F. Associative Anamnesis. Psychoanalyt. Quart., 8: 354, 1939.
DEUTSCH, F. The Production of Somatic Disease by Emotional Disturbance. Publicat. Assoc. Research Nervous and Mental Disease. Vol. XIX, pp. 271-292, 1939.
DEUTSCH, F. Studies in Pathogenesis. Biological and psychological aspects. Psychoanal. Quart. 2: 225, 1933.
DEUTSCH, F. Psychological Methods of Obtaining Medical Information. Acta Orientalia, 1946.
18. RACKEMANN, F. Progress in Internal Medicine. Arch. Intern. Medicine. 77: 6, 1946.
19. WOLFE, H. Z. Pres. Pub. Assoc. Res. Nerv. and Ment. Dis. 19: 330, 1939. Cambridge, Mass. 1943. Williams & Wilkins, Baltimore, 1939.
20. DANIELS, G. E. Psychosom. Medicine 2: 276, 1940.

THE USE OF THE PSYCHOSOMATIC CONCEPT IN SOCIAL CASE WORK

ELEANOR E. COCKERILL

The social caseworker who chooses a medical setting for the practice of her profession has an opportunity which brings both challenge and responsibility. It is challenging because she must be able to function as a social worker in a medical rather than a social work world. It brings responsibility because she must relate her social work knowledge and skills to the intricate processes of medical diagnosis and treatment which are basic in the attainment of the physician's primary purpose. Her contribution must be significantly related to this primary purpose of medical care and yet it must not lose its separate social work focus and purpose.

Throughout the history of medical social work there is evidence that it has frequently been difficult for departments of social service in hospitals to achieve this relatedness and also this separateness. Undoubtedly our own professional insecurity and our need to be accepted within this medical world were contributing factors in the relatively slow development of a sound professional focus for social work in hospitals. We were so anxious to be needed and useful that we readily accepted responsibilities which kept us occupied with activities that were appreciated by harassed administrators and busy doctors but did not help them to discover how to use us as social workers.

Changes within medicine itself have increased the specialized resources of help for the ill person and today his medical treatment may utilize the skill of several experts. Whether the multiple services of this group of professional persons can be as meaningful to the patient and as effective in bringing about his recovery as the care of a single physician depends to some degree at least upon the capacity of the group to achieve a unified approach to the problem of the patient. This means, among other things, a sharing of knowledge and understanding about the patient by all of those concerned with his care, with each expert using his own special skill in relation to one aspect of his problem.

Medical social workers appreciate the increasing degree to which

physicians are achieving competence in the recognition and evaluation of the social component in illness. Psychiatrists, a specialized group within medicine, have voiced their approval of the further integration within general medicine of psychiatric concepts and methods. Physicians have long emphasized the social worker's need to have certain basic knowledge about disease and its treatment and the psychiatric group has been active in its efforts to broaden the social worker's understanding of the dynamics of human behavior. As this fusion and interchange of experience and knowledge becomes intensified it is essential that each professional person recognize that the purpose of this sharing is to help him to do his own particular job better rather than to take on the responsibilities of another professional person. If the medical social worker, for example, attempts to incorporate incompetently the psychiatrist's method of helping she may not make available to her patient the social work services which she is prepared to give skillfully and also fail to help the patient to make use of what the psychiatrist has to offer. If the physician undertakes to carry through the social work services which his patient needs, he may overlook essential medical services and also fail to make available the specialized help of the medical or psychiatric social worker. This focusing of responsibility for the specialized aspects of a patient's total care, does not exclude the necessity for an awareness on the part of all members of the medical team of the various facets of the patient's problem.

Dr. Deutsch has focused our attention today upon the contribution of psychosomatic research to the understanding and treatment of disease. His paper has had meaning and significance for the social case workers in this audience but we have related what he has said to our own special area of professional interest and concern. The medical and psychiatric social worker's primary concern is not with the symptomatology of disease and the techniques of its treatment because the physician has responsibility for these aspects of a patient's problem and care. Her focus is upon the social factors which have helped to make the patient ill, the social problems which his illness creates for him and the obstacles which may limit his capacity to make use of what medicine has to offer. The social caseworker's frame of reference, thus, has been socially and not medically oriented

throughout the presentation by Dr. Deutsch. Our social casework concept that the individual reacts physically, intellectually and emotionally to the experiences he has as he moves through life has been deepened and given new meaning by the contribution of psychosomatic research. Our awareness that the behavior of an individual is purposive has been broadened to include the concept that "body behavior" is also expressive of the individual's way of resolving conflict. As we achieve understanding of the purpose served by illness we are able to appreciate more fully why some of our patients cannot afford to give up their physical symptoms until some more satisfying solution of their emotional conflict has been achieved. The findings made available through the psychosomatically oriented exploratory process described by Dr. Deutsch have helped us to appreciate more fully the intricate operation of the unconscious and the skill which underlies the elicitation and use of such material. We are again made aware of the precise and thoroughgoing methods of medical science as it steadily moves ahead toward greater understanding of the causes of disease and greater skill in its treatment. We have been given, through this presentation, new insight about the significance of past and current life situations which are shared with us in our own professional relationship with patients. We have been helped to recognize that tension and anxiety created by the demands made by the social environment are the outgrowth of inner as well as outer pressures. In other words, the primary contribution of psychosomatic research to the field of social casework is the more complete understanding it is bringing about the "what" of the patient's problem. It remains for us, as social workers, to define how this deepened understanding may enrich our own social work services. We cannot look to medicine for this because our function is not to offer medical therapy but rather social casework help which is both related and different.

When I define the specific professional responsibility of the medical or psychiatric social worker as that of helping the patient and his family to be more responsible in their use of the physician's services, I am really saying that a primary objective of her service is to enhance the usefulness of medical care to the patient and to help the hospital to achieve its purpose in medical treatment. I am aware that this concept is one which has provoked some criticism by the medical

profession. It has been pointed out that medical treatment is offered within the medium of the doctor-patient relationship and that if there are problems related to it the doctor, not a third person, should help to resolve them. This is a valid interpretation of the doctor's responsibility. However, there are problems in using the doctor's help which the patient may not bring to this relationship and which may even keep him from taking hold of the help the doctor can give. For example, many patients are unable to take the initial step of going to the psychiatrist without help and some retreat after the first interview because of the fears associated with psychiatry. This is especially true of the patient who finds the transition from a somatic to an emotional focus difficult. He may need a good deal of help from both physician and social caseworker before he can use this form of treatment which seems initially less useful to him than medication or some other therapeutic agent upon which he has become dependent. Dr. Deutsch has found this to be true in his own experience and he has emphasized that the social worker can render a valuable service to both patient and psychiatrist through giving this help.

Perhaps the largest number of requests from physicians for the professional help of the social worker are related to the need for more complete understanding of the social situation of the patient. Often this referral is made on the basis that the doctor does not have the "time" to explore this facet of his patient's problem. This is an unfortunate emphasis if it means that the physician is delegating this task to someone else just because he is too busy at the moment to investigate this aspect of the patient's need for help. Actually, the physician should take the initial responsibility for identifying the social component and the need for further exploration of it just as naturally as he takes responsibility for identifying the need for other special services. His referral to the social worker should not be contingent upon how much time he has but rather upon the fact that his own professional evaluation of the problem has pointed toward the need for the special skill which the social worker can bring and which he, as the doctor, actually does not possess. It is the social workers' responsibility to bring to the patient or his family her own professional knowledge and skill which will be productive, not of something better than the doctor's appraisal of the social component, but rather some-

thing different than he has perceived as the physician. The social worker sees herself not as a competing member of the medical group but rather as a contributing one.

The preparation of a social history has long been an accepted function of both medical and psychiatric social workers. We have sometimes questioned the degree to which this contribution from us has been utilized because it has often seemed that the medical care of the patient was not related to his actual social situation. We have noted in recent years, however, that our social studies have not only been read by physicians but that the understanding about the patient which we have been able to offer has actually been a part of the total body of knowledge upon which medical treatment has been formulated. As we have become more competent as social workers we have been able to carry on this function with greater satisfaction to ourselves and our medical associates and with an increased use of it as a means of bringing social work help to the patient. Initially we were so intent upon meeting the physician's desire for social data about his patient that we failed to utilize a very real opportunity to make this process of fact-finding a meaningful and helpful part of the patient's medical care. We were often made aware of our limited contribution by the physician, himself, who after reading our comprehensive social study would inquire concerning what we had been able to do about the social problems we had so aptly described. The medical or psychiatric social worker of today accepts the doctor's request for a social study as an appropriate use of her help. However, she has come to see this function as a more inclusive and dynamic service for the patient than the collection of data about him and the presentation of these to his physician. To clarify the nature of this broader service to the patient is the purpose of the balance of this discussion.

Dr. Deutsch has been associated professionally with both medical and psychiatric social workers and he has discussed with me the help they have been able to give through making available to him certain important social data about the patient. He has provided an outline for these social workers of the various types of social information which is significantly related to the patient's illness. He emphasizes the fact that his purpose in making the outline available is not to provide the questions the worker is to ask but rather to increase her

understanding and awareness of the type of social material which will be useful to him as the psychiatrist. He does not anticipate that the material which the patient contributes during the psychiatric interview will parallel that which he has presented to the social worker. This difference in the content of the two interviews is not due to the patient's conscious misrepresentation of the situation but rather it is related to the difference in the equipment of the two interviewers, and in their purpose, focus and method.

I am aware that this different use of interviewing skill by the social caseworker is not fully understood by the medical profession. During recent years our emphasis upon the fact that we do not always make a home visit as a part of a social study but we may depend entirely upon our interviews with the patient or a member of his family group in the clinic or hospital has led to some concern about this trend in our practice. It has seemed that we were attempting to be psychiatrists especially when our social studies have included references to feelings and attitudes which have been shared with us by the patient or his family. Also we have sometimes used psychiatric terms in our description of the patient's reaction to his illness and the demands which it imposes upon him. Our social studies, perhaps, have seemed to emphasize the emotional factors in the situation more than the reality factors of income and rent and housing. Does this mean that the social caseworker is trying to take over the function of the psychiatrist or does it mean that she has grown in her capacity to see her patient as a person who does react physically, intellectually and emotionally to the experiences he encounters as he moves through life? Were our earlier routine home visits as productive or real understanding of the significance for the patient of his home environment as our present use of what the patient, himself, is able to share with us about his home and relationships within his family? Medical and psychiatric social caseworkers still make home visits but this is not a routine procedure in the sense that every family is visited in order that we may get a first hand view of the patient's home situation. The home is the patient's citadel and he may not wish to have it invaded. The fact that he is ill and dependent upon us for medical care does not mean that we are welcomed visitors in his home, at least not until he, himself, can see some real purpose in our visit and becomes a part of it

through asking us to extend our interest in him beyond the hospital and into his home. When he, himself, is an active participant in the planning for our visit to his home he is much more receptive to the help we offer to him in relation to some of the problems he is experiencing at home.

In the last analysis it is the patient, himself, who has to manage this problem of illness and we are dependent upon what he, with his inner and outer resources, is able to do with the help we extend. Physicians accept the fact that medical therapy is effective to the degree that the patient is responsive to it. The "uncooperative patient" makes us aware of the fact that the patient may not be able to engage himself in the processes of medical care. When he does not choose to carry out the steps which are outlined for him, medical therapy is obstructed. Actually, the patient has this right to choose but our acceptance of this fact does not relieve us of the responsibility for extending help to him with the problems which add to his uncertainty about the choices he has to make.

It is often around this problem of making a decision that the social caseworker's help is most needed by the patient. This is not true of all patients, of course, because many are able to relate to the authoritative direction of the physician and feel relieved of the responsibility for making a decision themselves. Others, however, show an inability to accept the doctor's guidance and initially use their energy in fighting or rejecting his help.

Mrs. A. was a patient who felt that she might lose more than she would gain through completing her medical examination and thus was resisting the step of having a chest x-ray. The social caseworker had been requested by the physician to explore the social factors in her situation because it seemed probable that she had active pulmonary tuberculosis. In the beginning of the interview, Mrs. A. said quite frankly that she was almost certain the x-ray would show that she had tuberculosis and she would prefer not to know the truth about her condition. Having recently married, she wasn't "willing to have any doctor interfere with my plans." She felt the doctor might have given her a diet or a tonic but he had refused to do this until the x-ray was taken. Mrs. A. admitted that she had lost weight, felt tired all of the time and had little appetite. She thought she had been working

too hard getting settled in her new home and that all she needed was a tonic and a diet. She was sure she could find a doctor who would prescribe these but if not she would buy something at the drug store. The social caseworker commented that although Mrs. A. had come to the doctor for his professional help she seemed to have made her own diagnosis and decided upon the kind of treatment she needed. Mrs. A. was thoughtful for a moment and then replied that she did appreciate the doctor's interest in her but she was afraid that he would tell her to go to a sanitarium and that would mean the end of everything. With the caseworker's help she was able to talk about how much it had meant for her to have a home of her own and how she was looking forward to motherhood. She wondered how her husband would react to the news of her illness and whether he might become discouraged and leave her. The caseworker agreed that there did seem to be some reasons why she might not want to go ahead with her examination but wondered whether she might not also wish to take advantage of the doctor's help. Mrs. A. replied that if she actually did have tuberculosis she would probably get worse unless she did something about it and then all of her plans for the future would be ruined. She began to cry and said that she could not understand why this had to happen to *her*. For several minutes she talked about the "bad breaks" she had had during her life. The caseworker listened to Mrs. A's account of a long series of disappointing and frustrating life experiences. She agreed that there was a real reason why Mrs. A. might want the rest of her life to be different. There did seem to be something she could do about this particular crisis which might help her to eventually have the home and children she desired. Mrs. A. said she had started out to do something about it when she had come to the doctor but it just seemed to be more than she could manage. The caseworker agreed that it was hard to face the whole thing at once and really the doctor hadn't asked her to do that. Mrs. A. nodded and said that he had only asked her to have an x-ray of her chest. With some further help from the caseworker, Mrs. A. decided that even though she was afraid of the outcome she did want the doctor's help and that she could not have this unless she carried through the diagnostic procedures he had requested. She said she would carry out these steps and then see what she could do from that point on. The case-

worker described the type of help she might be able to give her at a later point when she might have to make some changes in her life and Mrs. A. said she would keep in touch with her.

The social caseworker, throughout this interview, was not unaware of the immaturity with which Mrs. A. was facing this dilemma in her life nor was she insensitive to the reality factors which made it so threatening. She noted, as Mrs. A. related her life story, a need to project blame upon others and limited insight about her own part in the various crises she had experienced. It seemed possible that Mrs. A. had suffered from the lack of love and affection throughout her life just as she had also suffered from the lack of proper food and healthful surroundings. All of these factors had relevance for the social caseworker as a part of her understanding of Mrs. A's reaction to the doctor's request for an x-ray but her professional responsibility was to help Mrs. A., with all of the limitations she had, to evaluate the situation more realistically and thus avail herself of medical help.

The professional service of the medical social worker is often utilized by the physician who has responsibility for the treatment of the patient with a gastrointestinal disorder. Miss S. had a series of hospitalizations and had achieved a fairly satisfactory recovery from the stomach symptoms which had necessitated medical and nursing care for a long period of time. She was eager to be self-sustaining and expressed reluctance about returning to her home and again becoming dependent upon her mother and sisters. Her physician felt that an opportunity to work and a satisfying work experience were important aspects of the help Miss S. would require in order to return to a functioning level again. In her interview with the caseworker, Miss S. again emphasized her hope that she would not have to be dependent upon her family. She felt that she really should be supporting her mother and sisters because they, too, were ill and unable to care for her. The case worker was impressed by the difference between this expressed wish of Miss S. to be more adequate and strong and the reality that her illness, which had made her dependent upon others for so long, had been characterized by many recurrences of the symptoms which put her to bed. She was aware that Miss S. probably had limited capacity to carry heavy responsibility and yet an opportunity to work was important for her. She noted, with interest, the fact that the patient felt her illness began when she was unable to complete her preparation to

become a nun because of an accident which made it impossible for her to go on. Miss S. said that she had felt very secure in the environment of the convent and she had never been well since she had had to give up this experience. Her family had been disappointed, too, because they wanted her to be a nun. She felt they had been critical of her failure to realize this ambition. The social caseworker helped Miss S. to talk about the kind of working situation in which she felt she would be happy and comfortable as well as self-sustaining and contributing. Quite readily, Miss S. shared her wish to work in a rectory. She said she had often thought about this possibility but had rejected it because she really should find a job where she could earn more and take care of her family. The caseworker said she could understand why it would seem this way to her but she wondered whether Miss S. might be able to begin in a less ambitious way to do this. Miss S. smiled and said that her doctor had told her she must not work too hard and he probably knew what was best for her. She agreed that she could think about earning more money when her doctor felt she was strong enough to work in a factory or something of that sort. Miss S. wondered whether the worker might be able to help her find a position as housekeeper in a rectory. She was offered this service and subsequently did carry through, with the social caseworker's help, the steps which were necessary. She was symptom free for nearly a year and then appeared in the clinic with a mild recurrence of her symptoms. Inquiry revealed that there had been a change in the staff at the rectory and that Miss S. was having difficulty in getting along with the new person who was supervising her work.

Neither Miss S's physician nor the social caseworker was surprised when she returned to the clinic at this point in her life when she was having to adjust to a less supportive environment. They continued their medical and social work services with the full realization that Miss S. was essentially a dependent person and that when her environment made demands upon her which she was unable to meet she would again have a need to use her symptoms as a means of managing. Her return to the clinic for further help was regarded, not as evidence that she could not be a socially useful person, but rather as evidence of the fact that she might continue to need help when confronted by demands which exceeded her capacity for meeting them.

Realistically many individuals do have this problem of having to

meet the experiences of life with limited physical and emotional resources. There is need for all of us to be as creative and responsible in the use of our knowledge and skill in the rehabilitative phase of medical care as we are in the curative phase. Psychosomatic research has a good deal to offer social caseworkers in terms of understanding of the emotional needs which handicapped persons bring to the experience of meeting the reality demands imposed upon them by their chronic disease. In the case of the diabetic patient, for instance, psychosomatic research has suggested the possibility that the patient may be limited in his capacity to assume the degree of responsibility required by a diabetic regime because of his basic need to be dependent. We are not always aware of this possibility, particularly when we confine our evaluation of the diabetic patient's capacity to manage the regime outlined for him to a consideration of his intellectual equipment and economic resources. Many diabetic patients are able to grasp intellectually the dietary requirements of their disease and yet are unable to assume responsibility for the control of what they eat. Others learn how to use the insulin syringe quite readily and yet are reluctant to be responsible for this aspect of their daily routine. In fact, many of these patients seem to depend a great deal upon their relationship with the person who administers the insulin. Social caseworkers have observed that a premature termination of their own helping relationship with the diabetic patient may be followed by a progressive lessening of his ability to manage his regime. We need to be aware of the fact that the benefit of the physician's knowledge about diabetes and its control and the value for the patient of the specific routine worked out by his doctor may be lost entirely if we are not sensitive to the patient's need for supportive help at the point when he must assume such a high degree of responsibility for his own care. Too often the social caseworker has terminated her help when it has seemed certain that the diabetic patient understood his diet, when he has learned how to use his syringe and has assured those concerned with his care that he can purchase insulin and proper food. It has often seemed that the basic essentials have been met and that the patient is equipped with the things he needs for the experience of living with diabetes. Actually, he may need the help of the social caseworker at the point when he takes on this new responsi-

bility more than at any other time because of what she can offer in terms of support, recognition and encouragement.

The social caseworker's service to the patient who has to cope with the problem of living with chronic disability often includes the use of employment and vocational resources within the community. Psychosomatic research has contributed to the social worker's understanding of the emotional needs which handicapped persons bring to the reality experience of utilizing special employment opportunities and other services designed to help them cope more adequately with the problem of living with a damaged heart or stiff joints or a psychoneurosis. This understanding will enrich our services through helping us to be more sensitive in our selection of the resources within the community which will have maximum usefulness and benefit for the patient. A sheltered workshop, for instance, may impose emotional strain upon the patient whose need for status and recognition may not be met in this protected situation. A position as an elevator starter may have infinitely more emotional value for the individual who needs to be the "boss" than a job as the operator of an elevator. As we noted in the illustration of Miss S., it was important for her to be helped to find an employment situation which would meet her emotional, as well as her economic needs.

The problem of physical restoration, with all that this includes in its broadest sense, is the responsibility of medicine and its specialties. The social caseworker's task is that of helping the individual to make the best use that he can of himself and his potentialities within the social world of which he is a part. The future holds rich promise for increased effectiveness on the part of both medicine and social work as we continue to grow in understanding and in our professional capacity to help individuals face the problem of disease and cope with the impact of it upon his living.

THE ELIMINATION OF POLIOMYELITIS VIRUS FROM THE HUMAN MOUTH OR NOSE*

ROBERT WARD, M.D. AND BURRILL WALTERS, B.A.

*From the Department of Pediatrics, New York University, College of Medicine, and the
Children's Medical Service, Bellevue Hospital*

The precise pathways pursued by poliomyelitis virus in travelling from the infected host to the susceptible individual have not been clearly defined. Although there is considerable evidence in favor of the intestinal-oral circuit, the respiratory channel (droplet infection) has not been discarded from consideration as an important mode of transmission.

This paper reports an experiment designed to answer the question: Can poliomyelitis virus be eliminated from the mouth? The question is asked because, although poliomyelitis virus has been recovered from washings of the nasopharynx (1-6), and oropharynx (3) (7) (8), from swabs of the pharynx (9) (7), and from the pharyngeal wall with or without the tonsils (10-14) there is no published evidence that it is actually expelled from the mouth under natural conditions. Indeed, a previous study failed to detect virus in saliva and oral secretions of 20 patients in the first two weeks of paralytic disease (15).

MATERIAL AND METHODS

Tests were carried out on material from 19 patients in the early stages of poliomyelitis acquired in an epidemic during the summer of 1945¹. Because Howe and his associates were able to isolate poliomyelitis virus with considerable frequency (43%) from pharyngeal swabs taken during the first three days of illness and not thereafter (9), this early phase was thought to be perhaps one of critical epidemiological importance, and therefore worth emphasizing in the present study.

Collection of Material

Material was obtained from 13 patients on the second, from 5 on the third, and from one on the fourth day of illness. Eight patients exhibited weakness

*Aided by a Grant from the National Foundation for Infantile Paralysis, Inc.

¹Many thanks for their assistance are due to Dr. Frederick P. Lee, Health Officer of Paterson, New Jersey, Mr. Thomas Tonge, Superintendent of the Paterson General Hospital, and Dr. William A. Dwyer, Physician-in-Charge of the Passaic Isolation Hospital.

or paralysis at some time, and 11 had an illness compatible with non-paralytic or abortive poliomyelitis (Table 2).

Firstly, a sterile cloth mask was tied over the patient's mouth and nose for one-half hour during which he was induced to talk, blow, cough and expectorate into the mask. Most of the subjects cooperated so that the mask became visibly wet. The central wet portion was then cut out with sterile instruments and placed in a sterile lusteroid tube containing one ml. sterile distilled water. Secondly, the nose was swabbed with two sterile cotton swabs² and lastly two swabs of the tonsillopharyngeal area were taken and similarly stored. These materials were either frozen immediately with solid CO₂, or refrigerated for one or two hours and then stored in the frozen state until prepared for inoculation.

Preparation for Inoculation

Before attempting to extract human virus from the masks, a preliminary experiment was designed to test the proposed method. Since it was important to know if *minimal* quantities of virus could be detected on the mask, titrations of a poliomyelitis-like virus³ pathogenic for mice were carried out after the virus had been added to sterile cloth masks of the same type used in the human tests. Extracts of masks made with distilled water were compared to masks extracted with a 0.0001 normal sodium carbonate solution at pH8 and adjusted to about pH4 before inoculation. The latter procedure was patterned after that described by Wenner for the elution of Lansing virus from cotton swabs (16). Thus, serial ten-fold dilutions of a 10% suspension of infected mouse brain were prepared in sterile distilled water. Starting with the 10% suspension, 1 ml. of each dilution of virus was pipetted on to each of 2 masks. One mask was extracted with 9 ml. of distilled water and the other with 9 ml. of sodium carbonate solution at pH8. This was repeated with each concentration of virus, so that the final theoretical concentrations of virus in the extracts were 10⁻², 10⁻³, 10⁻⁴, 10⁻⁵, and 10⁻⁶. Control titrations of virus in distilled water and in sodium carbonate solution at pH8 were carried parallel with the mask extracts. The results are shown in Table 1. Extraction of masks at pH8 was clearly superior to extraction with distilled water and when compared with the control suspensions (no mask), showed practically no loss of virus. Hence this method was adopted for the preparation of the human materials.

Each mask used in the human test was shredded with scissors and to it was added 8 ml. of a sterile 0.0001 normal sodium carbonate solution at pH8, pounded briefly in a mortar, and the fluid expressed by means of a 50 ml. syringe with a copper wire gauze inside the barrel covering the nozzle. This was designated the *first extract*. It was centrifuged in an angle head (New International) at 4,000 R.P.M. for one-half hour. To the supernatant fluid was added 15% anaes-

²Each nasal passage was entered to the depth of 1 to 2 inches. No attempt was made to reach the nasopharynx.

³Immunologically closely related to Theiler's FA strain.

thetic ether and the mixture was shaken and stored overnight at 3°C. The following day the ether was removed by bubbling air through the extract; the pH was adjusted to about 4 by the addition of 2% acetic acid and the material was inoculated into two monkeys by the intracerebral route. The *second extract* was prepared immediately after the first by adding to the mask another 8 ml. of sodium carbonate solution at pH 8 and expressing it in the same fashion. To this extract was added the sediment obtained from the first centrifugation, and the mixture was given intranasally to the same monkeys.

The nasal and pharyngeal swabs were prepared in the same fashion, 2 ml. of sodium carbonate solution being used to extract them. Cultures of all the etherized materials were usually sterile.

TABLE 1

Titration in Mice of Poliomyelitis-like Virus in Masks Extracted With a) Sodium Carbonate Solution at pH 8 Compared With b) Distilled Water*

SUSPENSION	FINAL CONCENTRATION OF VIRUS					LD 50 TITRE (LOG OF DILUTION)
	10 ⁻²	10 ⁻³	10 ⁻⁴	10 ⁻⁵	10 ⁻⁶	
Control, dist. water.....	6/8†	8/8	8/8	4/8	2/6	5.2
Control, pH 8.....	7/7	8/8	8/8	8/8	1/8	5.6
Mask extract, pH 8.....	8/8	8/8	7/8	6/8		5.2 or more
Mask extract, dist. water.....	8/8	6/8	3/8	0/8		3.6

* The virus used in this experiment was pathogenic for mice and immunologically closely related to Theiler's FA strain.

† Numerator equals number of mice exhibiting signs of CNS involvement, denominator number inoculated.

Inoculation of Monkeys

Immature rhesus monkeys (*Macaca mulatta*) weighing 3 to 5 kilograms were used throughout. Intracerebral inoculation was performed under ether anaesthesia, the inoculum varying between 1 and 2 ml. Two monkeys were employed to test each of the masks, and one monkey for each of the nose and throat swabs, respectively. Most of the animals receiving the mask extracts were reinoculated after 1 or 2 weeks if no signs of illness had appeared before. It was felt that these procedures would favor the detection of virus in the mask, should any be there.

The second extract (unetherized), plus the sediment from the first extract, were instilled intranasally (1 ml. in each nostril) daily for two days in respect to the mask and for one day in respect to the nose and throat swabs. The olfactory bulbs of all monkeys were examined and typical lesions of poliomyelitis were found in the bulbs of the two animals inoculated with the mask extract of patient #2 (Table 2), suggesting that the nasal administration may have helped to secure positive results.

Criteria for the Detection of Poliomyelitis Virus

The diagnosis of poliomyelitis in the monkey was made on exhibition of weakness or paralysis of one or more extremities confirmed by characteristic histological lesions in the central nervous system (CNS)—namely, necrosis of nerve cells, neuronophagocytosis, and perivascular cellular infiltration. Paralyzed monkeys

TABLE 2

Results of Tests for Poliomyelitis Virus in Material from Nose and Throat

PATIENT	AGE (YEARS)	TYPE OF ILLNESS	NO. WBC IN CSF	DAY OF ILLNESS	VIRUS DETECTED IN		
					Throat	Nose	Mask
1	13	P*	360†	2	0/1‡	1/1	1/2
2	4	P	N.D.§	2	1/1	0/1	2/2
3	2	P	36	2	1/1	0/1	0/2
4	7	NP	50	2	1/1	0/1	0/2
5	17	NP	0	2	1/1	0/1	0/2
6	8	NP	61	2	1/1	0/1	0/2
7	5	NP	59	3	1/1	0/1	0/2
8	7	P	58	2	0/1	0/1	0/2
9	5	P	60	3	0/1	0/1	0/2
10	4	P	34	3	0/1	0/1	0/2
11	14	P	B¶	3	0/1	0/1	0/2
12	4	P	N.D.§	4	0/1	0/1	0/2
13	21	NP	3	2	0/1	0/1	0/2
14	8	NP	466	2	0/1	0/1	0/2
15		NP	0	2	0/1	0/1	0/2
16	9	NP	7	2	0/1	0/1	0/2
17	15	NP	8	2	0/1	0/1	0/2
18	11	NP	80	2	0/1	0/1	0/2
19	4	NP	5	3	0/1	0/1	0/2

* P = paralytic.

NP = non-paralytic.

† Number of white blood cells in the cerebrospinal fluid.

‡ Numerator: number of monkeys positive clinically and pathologically for poliomyelitis. Denominator: number of monkeys inoculated.

§ N.D. = no spinal fluid cell count recorded.

¶ Lumbar puncture resulted in a bloody tap.

were sacrificed soon after the appearance of paralysis, all others between 5 and 6 weeks after inoculation. Histologic examination of the latter brought to light no examples of non-paralytic poliomyelitis. Portions of the CNS of the monkey paralyzed after receiving extract of mask of Patient No. 1 were passaged to a second monkey, to 10 mice, and 3 guinea pigs. The monkey developed typical poliomyelitis while the other animals remained negative.

RESULTS

Poliomyelitis virus was detected in the masks of two of the 19 patients (Table 1). This finding indicates that it can be expelled from the mouth or nose at least in some patients under the circumstances described. In one of these patients (# 1) virus was also recovered from the nasal swabs, and in patient # 2, from the pharyngeal swabs. Virus was isolated from the pharyngeal swabs alone in 5 additional subjects. All tests were negative on the 12 remaining individuals.

Virus was found, with one exception, in materials obtained on the second day of illness from patients 3 of whom had paralytic and 4, non-paralytic poliomyelitis. Although both positive masks were derived from paralytic patients, the numbers are too small to attach any significance to this finding.

DISCUSSION

The recovery of poliomyelitis virus from cloth masks into which patients had expelled material from the mouth and nose indicates that virus can be eliminated, at least under the conditions of this experiment, from the mouth or nose. This is believed to be the first demonstration of virus elimination from these portals under circumstances which come fairly close to being natural. An important question is: What is the epidemiologic significance of this finding? Or, in other words, does this mean that the disease is transmitted by droplet infection? The answer obviously cannot be given in straightforward terms since many pertinent facts are still unknown. One might argue that the demonstration of elimination of virus from the mouth or nose supports the theory of *contact infection*, for which circumstantial evidence has been described recently by Ayccock, et al (22) and by Casey and associates (23). On the other hand, if infection were usually acquired by aspiration of droplets it is not unreasonable to suppose that the nasal pathway, in particular the olfactory, would be utilized. That this does not usually appear to be the case has been amply demonstrated (17) (13) (18) (14) (19). The failures to detect virus in the human nasal mucosa (13) and the experiments in which nasal chemoprophylaxis failed to alter the incidence of the disease (20) (21) may be cited as additional evidence against any part of the nasal mucosa

serving as the area of primary attack. It is conceivable that virus, although aspirated by way of the nose, may actually penetrate the mucous membrane of the pharynx or lower alimentary tract.

Although contact infection seems to occur in some cases of poliomyelitis, the nature and degree of contact necessary for transmission are unknown. To many the term "contact" implies "respiratory contact" or droplet infection. It should be remembered that, generally speaking, contact infection can also take place along other channels, for example, the intestinal-oral.

The present experiment was undertaken with the expectation of negative results. It was felt that the balance of evidence pointed away from poliomyelitis being spread like a respiratory disease. It seemed that the presence of virus in the pharynx and its absence from the nose might conceivably have an analogous epidemiologic significance to that described by Hamburger et al in regard to the streptococcus (24). These authors have shown that the "dangerous" carriers of the hemolytic streptococcus (i.e. those individuals who discharge organisms into the air), are the *nasal* carriers in contrast to the pharyngeal carriers who are not "dangerous". The frequency of elimination of poliomyelitis virus from the mouth or nose is unknown, for the number of tests in the present report and the methods employed for detection of virus may both be inadequate. Nor has any attempt been made in this study to determine if virus is eliminated from these portals at still earlier or later stages of infection.

Lastly, the recovery of virus from the nasal swab of one patient (§ 1, Table 1) whose mask was also positive is open to several interpretations: a.) virus was present and multiplying in the nasal mucosa, b.) the swab had penetrated as far as the nasopharynx and virus was obtained from the pharyngeal component, and c.) virus was in the nasal passage as a result of being aspirated from the mask or expelled from the pharynx. Recent evidence (13) (14) (15) is against (a). The technique employed in swabbing the nose while not precluding it, makes (b) unlikely. Inasmuch as the nose was swabbed *after* the mask had been in place for some time during which forceful expulsion of material from the throat was taking place, the third possibility appears to us as the most likely. It is recognized that no virus was obtained

from the throat swab in this case but perhaps that may be explained on the use of only one monkey for the test (25).

SUMMARY

1. Poliomyelitis virus has been demonstrated in material expelled from the mouth (or nose) of two patients out of 19 studied. This was achieved by having patients blow and spit into cloth masks from which virus was extracted.

2. Virus was also detected in nasal swabs of the first patient and pharyngeal swabs of the second patient shown to have eliminated virus from the mouth or nose.

3. In five additional patients virus was isolated only from swabs of the pharynx.

4. Certain implications of these findings have been discussed. It is to be emphasized that their epidemiological significance or insignificance is yet to be determined.

BIBLIOGRAPHY

1. KLING, C., WERNSTEDT, W., AND PETERSSON, A.: Recherches sur le mode de propagation de la paralysie infantile épidémique (maladie de Heine-Medin) Deuxième Memoire, Ztschr. F. Immunitätsforschung und Exper. Therap. 12: 316, 657, Jan. 1912, Mar. 1912.
2. FLEXNER, S., CLARK, P. F., AND FRASER, F. R.: Epidemic Poliomyelitis: Fourteenth Note: Passive Human Carriage of the Virus of Poliomyelitis; J.A.M.A. 60: 201, Jan. 18, 1913.
3. PAUL, J. R., AND TRASK, J. D.: The Detection of Poliomyelitis Virus in so-called Abortive Types of the Disease, Jour. Exp. Med. 56: 319, Sept. 1932.
4. PAUL, J. R., AND TRASK, J. D., AND WEBSTER, L. T.: Isolation of Poliomyelitis Virus from the Naso-Pharynx, Jour. Exper. Med. 62: 245, Aug. 1935.
5. VIGNEC, A. J., PAUL, J. R., AND TRASK, J. D.: The Recovery of the Virus of Poliomyelitis from Extra-Neural Sources in Man, with a Summary of the Literature, Yale J. Biol. & Med. 11: 15, Oct. 1938.
6. KRAMER, S. D., HOSKWITH, B., AND GROSSMAN, L. H.: Detection of the Virus of Poliomyelitis in the Nose and Throat and Gastro-Intestinal Tract of Human Beings and Monkeys, J. Exp. Med. 69: 49, Jan. 1939.
7. HORSTMANN, D. M., MELNICK, J. L., AND WENNER, H. A.: Isolation of Poliomyelitis Virus from Human Extra-Neural Sources. I. Comparison

- of Virus Content of Pharyngeal swabs, Oropharyngeal Washings, and Stools of Patients, *J. Clinical Invest.* 25: 270, Mar. 1946.
8. MELNICK, J. L., HORSTMANN, D. M., AND WARD, R.: Isolation of Poliomyelitis Virus from Human Extra-Neural Sources. II. Comparison of Virus Content of Blood, Oropharyngeal Washings, and Stools of Patients, *Jour. Clin Invest.* 25: 275, Mar. 1946..
 9. a. HOWE, H. A., WENNER, H. A., BODIAN, D, AND MAXCY, K. F.: Poliomyelitis Virus In the Human Oro-Pharynx, *Proc. Soc. Exp. Biol. & Med.* 56: 171, June 1944.
b. HOWE, H. A., BODIAN, D, AND WENNER, H. A.: Further Observations of the Presence of Poliomyelitis Virus in the Human Oro-Pharynx, *Bull. J. H. Hosp.* 76: 19, Jan. 1945.
 10. LANDSTEINER, K., LEVADITI, C., AND PASTIA, C.: Recherche du virus dans les organes d'un enfant atteint de poliomyélite aiguë. *Compt. Rend. Acad. Sc.* 152: 1701, June 12, 1911.
 11. FLEXNER, S., AND CLARK, P. F.: Epidemic Poliomyelitis; Eleventh Note: Relation of the Virus to the Tonsils, Blood, and Cerebrospinal Fluid; Races of the Virus. *J.A.M.A.* 57: 1685, Nov. 18, 1911.
 12. FLEXNER, S., AND AMOSS, H. L.: Persistence of the Virus of Poliomyelitis in the Nasopharynx. *J. Exp. Med.* 29: 379, June 1919.
 13. SABIN, A. B., AND WARD, R.: The Natural History of Human Poliomyelitis: I. Distribution of the Virus in Nervous and Non-Nervous Tissues. *J. Exp. Med.* 73: 771, June 1941.
 14. KESSEL, J. F., MOORE, F. J., STIMPERT, F. D., AND FISK, R. T.: Occurrence of Poliomyelitis Virus in Autopsies, Patients, and Contacts, *J. Exp. Med.* 74: 601, Dec. 1941.
 15. SABIN, A. B., AND WARD, R.: The Natural History of Human Poliomyelitis. II. Elimination of the Virus, *J. Exp. Med.* 74: 519, Dec. 1941.
 16. WENNER, H. A.: Effect of H. Ion Concentrate for Eluting Poliomyelitis Virus from Cotton Fiber, *Proc. Soc. Exp. Biol. and Med.* 60: 104, Oct. 1945.
 17. SABIN, A. B.: The Olfactory Bulbs in Human Poliomyelitis, *Am. J. Dis. Child*, 60: 1313, Dec. 1940.
 18. HOWE, H. A., AND BODIAN, D.: Neural Mechanisms in Poliomyelitis, *The Commonwealth Fund*, N. Y. 1942.
 19. FABER, H. K., AND SILVERBERG, R. J.: A Neuropathological Study of Acute Human Poliomyelitis with Special Reference to the Initial Lesion and to Various Potential Portals of Entry, *J. Exp. Med.* 83: 329, April, 1946.
 20. TISDALL, F. F., BROWN, A., DEFRIES, R. D., ROSS, M. A., AND SELLERS, A. H.: Zinc Sulphate Nasal Spray in the Prophylaxis of Poliomyelitis, *Canad. Pub. Health J.* 28: 523, Nov. 1937.

21. ARMSTRONG, C.: Experience with Picric Acid-Alum Spray in the Prevention of Poliomyelitis in Alabama, *Am. J. Pub. Health* 27: 103, Feb. 1937.
22. AYCOCK, W. L., KESSEL, J. F., AND GORDON, J. E.: The Infectious Period of Poliomyelitis and Virus Detection, *A. J. Med. Sc.* 205: 454, Mar. 1943.
23. CASEY, A. E., FISHBEIN, W. I., AND BUNDESON, H. N.: Transmission of Poliomyelitis by Patient to Patient Contact, *J.A.M.A.* 129: 1141, Dec. 22, 1945.
24. HAMBURGER, M., JR., GREEN, M. J., AND HAMBURGER, V. G.: Problem of the "Dangerous Carrier" of Hemolytic Streptococci, *J. Inf. Dis.* 77: 68, July-Aug. 1945.
25. HOWE, H. A., AND BODIAN, D.: The Efficiency of Intranasal Inoculation as a Means of Recovering Poliomyelitis Virus from Stools, *Am. J. Hygiene* 40: 224, Sept. 1944.

PHYSIOLOGICAL STUDIES IN CONGENITAL HEART DISEASE*

I. PROCEDURES

R. J. BING, L. D. VANDAM, AND F. D. GRAY, JR.

From the Departments of Surgery and Pediatrics, The Johns Hopkins University and Hospital

Recent studies which led to the surgical treatment of the group of congenital heart disease with cyanosis, have stressed the physiological importance of diminished rate of pulmonary blood flow in the production of anoxemia (1). Varying types of congenital malformations of the heart with reduced volume of circulation through the lungs have been described. These include, first, cases with pulmonary atresia or stenosis, alone or in combination with other malformations to form the "tetralogy of Fallot"; second, those with a single ventricle in which the pulmonary artery arises from the rudimentary outlet chamber; and third, cases with truncus arteriosus, in which the circulation to the lungs courses through the bronchial arteries (1). It seemed of importance to study, quantitatively, the changes in pulmonary blood flow in these conditions in order to correlate this primary abnormality with accompanying hemodynamic and respiratory alterations. Furthermore, the severity and prolonged duration of anoxemia in individuals with reduced pulmonary blood flow provided an opportunity to investigate certain aspects of physiological adaptation to reduced arterial oxygen saturation. Finally, the practical significance of recognizing pulmonary stenosis and atresia preoperatively has made it advisable to study the diagnostic value of the physiological tests outlined below.

This communication deals with technical procedures employed in the study of congenital heart diseases belonging to the cyanotic group. Separate reports will be published which deal with preoperative findings in patients with reduced pulmonary blood flow, with postoperative findings in the same group, and with investigations in individuals with increased circulation through the lungs.

* This study was supported by a grant from the Commonwealth Fund.

The following procedures were employed: measurement of oxygen capacity and oxygen saturation of arterial blood; measurement of the oxygen and carbon dioxide content of blood obtained from peripheral arteries and from the cardiac chambers accessible to catheterization via the right side of the heart; determination of the rates of oxygen consumption and carbon dioxide elimination by indirect calorimetry; gas analyses of respiratory air under various conditions; and, finally, recording of arterial and intracardiac pressure curves.

Some of the data obtained were used for calculation of the blood flow through the lungs and the systemic circulation, and for estimation of the volume and direction of extra- and intracardiac shunts. These calculations in some instances involve assumptions which are of doubtful validity and it is realized that the resulting figures should be looked upon as no more than approximations. The actual data upon which the calculations have been based will be presented in the following papers. The succeeding paragraphs of this paper deal with the theoretical basis of the calculations and indicate some of the sources of error.

Measurement of the circulation through the pulmonary artery and the systematic circulation: According to Fick (2), the output of the heart may be calculated with the formulae:

1. Cardiac output (ml. per min.)

$$= \frac{\text{O}_2 \text{ intake (ml. per min.)}}{\text{O}_2 \text{ content of arterial blood (vol. per cent)} - \text{O}_2 \text{ content of mixed venous blood (vol. per cent)}} \times 100$$

or

2. Cardiac output (ml. per min.)

$$= \frac{\text{CO}_2 \text{ output (ml. per min.)}}{\text{CO}_2 \text{ content of mixed venous blood (vol. per cent)} - \text{CO}_2 \text{ content of arterial blood (vol. per cent)}} \times 100$$

During recent years Cournand and associates developed methods which permit the direct application of these formulae to the determination of cardiac output in man (3a). Samples of mixed venous blood from the right auricle or ventricle are collected by catheterization of these chambers and arterial samples are secured by direct puncture

of a peripheral artery¹. Blood gas values obtained by Cournand's methods provide valid figures for pulmonary blood flow only if the oxygen and carbon dioxide contents of peripheral arterial blood are identical with those in the pulmonary vein. In the majority of cardiac abnormalities, however, which were the subject of this investigation, admixture of blood resulted in arterial blood gas values which differed from those in the pulmonary vein. Consequently it was found necessary to derive values for oxygen and carbon dioxide concentrations of the pulmonary vein blood by indirect means. To accomplish this the following formula was employed:

$$3. \text{O}_2 \text{ content of pulmonary vein (vol. per cent)} = \text{percentage O}_2 \text{ saturation of pulmonary vein} \times \text{O}_2 \text{ capacity (vol. per cent)}$$

The percentage of oxygen saturation of the pulmonary vein blood was assumed to be 95 per cent. This represented an accepted value for normal individuals (4), and agreed with our analyses of pulmonary vein blood obtained through direct catheterization of that vessel in 4 cases with tetralogy of Fallot.

The carbon dioxide content of the pulmonary vein blood was derived from the alveolar concentration of this gas, the volume of the gas per 100 cc. of blood being obtained by plotting the tension on an oxygenated carbon dioxide absorption curve which was determined for each patient. The oxygen capacity was determined according to the method described in a subsequent paragraph.

The blood flow through the pulmonary artery was subsequently calculated with the equations:

4. Pulmonary artery flow (ml. per min.)

$$= \frac{\text{O}_2 \text{ intake (ml. per min.)}}{\text{O}_2 \text{ content of pulmonary vein (vol. per cent)} - \text{O}_2 \text{ content of pulmonary artery (vol. per cent)}} \times 100$$

¹ Formulae described in this paper include calculations of flows with both blood oxygen and carbon dioxide. In the succeeding reports, however, calculations based on blood carbon dioxide values will be omitted, since their accuracy has been found to be questionable (3b).

or

5. Pulmonary artery flow (ml. per min.)

$$= \frac{\text{CO}_2 \text{ output (ml. per min.)}}{\text{CO}_2 \text{ content of pulmonary artery (vol. per cent)} - \text{CO}_2 \text{ content of pulmonary vein (vol. per cent)}} \times 100$$

In normal individuals, sampling of blood from the pulmonary artery has been easily accomplished by catheterization (5). In the majority of patients with severe pulmonary stenosis, however, this procedure was impossible, since the catheter could not be passed through the narrowed lumen. In these cases gas values for right ventricular blood were substituted for those of the pulmonary artery. Large interventricular septal defects with shunting between the chambers made it probable that the concentration of blood gases in the right ventricle was not identical with that in the pulmonary artery, introducing an error in the estimation of pulmonary artery blood flow. A further difficulty in the calculation of the blood flow through the pulmonary artery by means of the Fick principle arose from the observation that some individuals, especially those belonging to the older age group, had developed a large collateral circulation to the lung as compensation for the pulmonary stenosis. In these cases, the quantity of oxygen consumed or of carbon dioxide released was too high in relation to the volume of blood which reached the alveolar epithelium via the pulmonary artery alone. This error in the calculation of pulmonary flow became greater as the ratio of collateral circulation to pulmonary artery flow increased. In pulmonary atresia, for instance, the total amount of oxygen diffusing through the alveolar epithelium was taken up by the pulmonary collaterals. In these cases, where pulmonary artery flow must be zero, values for pulmonary artery flow were obtained by calculation. This makes the recognition of pulmonary atresia impossible by the methods described above.²

² An attempt was made to overcome this difficulty in calculating pulmonary artery flow with formulae developed from mixing equations.

$$1. \quad \frac{(\text{PACO}_2 \times \text{PAF}) + (\text{CCO}_2 \times \text{CF})}{\text{PAF} + \text{CF}} = \text{PCCO}_2$$

$$2. \text{ PCF} = \text{PAF} + \text{CF}$$

These considerations made it evident that values estimated for the blood flow through the pulmonary artery in patients with tetralogy of Fallot and related conditions were approximations. They were, however, of sufficient accuracy to permit a preoperative diagnosis of pulmonary stenosis, although the degree of the stenosis could not be predicted with accuracy.

Measurement of systemic blood flow: The Fick principle was also applied in determining the blood flow through the systemic circulation. Because of the admixture of blood in hearts with interventricular septal defects, carbon dioxide and oxygen concentrations in right ventricular blood were not identical with true mixed venous blood. Although normally the blood entering the heart is not fully mixed until it reaches the right ventricle (6), right auricular samples had to be used in the calculation of systemic blood flow according to the formulae:

6. Systemic flow

$$= \frac{\text{O}_2 \text{ consumption (ml. per min.)}}{\text{O}_2 \text{ content of arterial blood (vol. per cent)} - \text{O}_2 \text{ content of right auricular blood (vol. per cent)}} \times 100$$

or

7. Systemic flow

$$= \frac{\text{CO}_2 \text{ production (ml. per min.)}}{\text{CO}_2 \text{ content of right auricular blood (vol. per cent)} - \text{CO}_2 \text{ content of arterial blood (vol. per cent)}} \times 100$$

Values for oxygen consumption and carbon dioxide production used in the above formulae refer to the oxygen consumed and carbon dioxide produced by the tissues. It can be assumed, however, that these values are identical with the oxygen uptake and carbon dioxide output in the lung.

where PACO_2 = CO_2 content of pulmonary artery; PAF = Pulmonary artery flow; CCO_2 = CO_2 content of collateral circulation; CF = Collateral flow; PCCO_2 = CO_2 content of pulmonary capillary blood; PCF = Pulmonary capillary flow.

Equation 1 solves for PAF and CF in terms of each other. Then, by substituting in equation 2, the absolute values are obtained. These formulae permitted calculations of pulmonary artery flow without using values for oxygen consumption. However they were abandoned since they relied upon carbon dioxide values of doubtful accuracy.

The systemic flow calculated with formulae 6 and 7 represents only the blood flow through the systemic circulation; it does not include the flow through the pulmonary collaterals, which originate from systemic vessels and course to the lung. These pulmonary collaterals do not share in the unloading of oxygen or the uptake of carbon dioxide in the tissues and contribute nothing to the total oxygen consumption or carbon dioxide production. Consequently, the amount of blood which courses through the aortic valves during systole (the aortic output) represents the sum of systemic flow and collateral circulation to the lung.

Determination of the total volume of blood perfusing the lung (pulmonary capillary flow): Clinical findings frequently indicated that pulmonary stenosis was accompanied by large collateral circulation or by a persistent ductus arteriosus. Consequently it seemed of interest to determine the total volume of pulmonary blood flow in order to compare it with the blood flow through the pulmonary artery. Here the Fick principle could be applied only if the concentrations of blood gases entering and leaving the pulmonary capillary bed were known. These values could be estimated by indirect means only. For this purpose the pulmonary alveolar space was employed as an aerotonometer for carbon dioxide in order to determine the concentration of this gas in the blood as it entered the pulmonary capillaries. After various unsuccessful attempts to obtain equilibration through the use of rebreathing methods a procedure was adopted which combined in principle the methods of Christiansen, Douglas, and Haldane (7) and of Field and his co-workers (8). Three anesthesia bags were filled with carbon dioxide and oxygen mixtures from specially prepared storage tanks. Since the partial pressure of carbon dioxide in the pulmonary capillary blood ranged from 25 to 40 mm. of mercury, the carbon dioxide contents of the bags were approximately 4, 5, and 6 per cent of carbon dioxide respectively, the remaining volume being composed of oxygen. The small difference between the carbon dioxide contents of the bags was necessary because it was found that equilibration was impossible if the carbon dioxide tensions in any bag differed more than 2 per cent from those of the pulmonary capillary blood. The total amount of gas in the bags was adjusted to conform to the vital capacity of the subject. After collection of expired air for measurement of the carbon

dioxide output the blood coming in contact with the pulmonary alveoli was equilibrated successively with the carbon dioxide of each bag. This was accomplished by requesting the patient to inhale the contents of the bag completely. After holding the gases in the lung for a period of 8 to 10 seconds, the equilibrated carbon dioxide mixture was exhaled into the bag by a forceful expiration. Special care was taken to assure maximal expiration in order to collect a representative sample of equilibrated lung air. If after analysis the final concentrations of carbon dioxide in the three bags were within .2 per cent of one another, it was assumed that equilibration had been reached. In several cases it was found necessary to re-equilibrate the bags several times, before their carbon dioxide contents reached satisfactory agreement. Alveolar air was then collected in order to determine the carbon dioxide content of pulmonary vein blood. This was accomplished by methods described later. To determine blood gas concentrations in volumes per cent the averaged final carbon dioxide tensions in the bags as well as the carbon dioxide tensions in the alveolar air were plotted on an oxygenated carbon dioxide *absorption* curve for the individual. Pulmonary capillary flow was then calculated according to the formula:

8. Pulmonary capillary flow (Total pulmonary blood flow) ml. per min.

$$= \frac{\text{CO}_2 \text{ output (ml. per minute)}}{\frac{\text{CO}_2 \text{ content of blood reaching alveoli (vol. per cent)} - \text{CO}_2 \text{ content of pulmonary vein blood (vol. per cent)}}{\text{CO}_2 \text{ content of pulmonary vein blood (vol. per cent)}}} \times 100$$

The principal source of error inherent in the determination of pulmonary capillary flow, by the method described above, lay in the possible occurrence of re-circulation of blood already in contact with the carbon dioxide in the bags (9). This could result in low calculated flows by raising the arteriovenous difference in formula 8. For this reason the results obtained with the method described above can only be accepted as approximations. The physiological and diagnostic value of this method, however, will become obvious in the succeeding papers.

Determination of shunts. Pulmonary capillary flow, as defined above, represented the amount of blood reaching the lung through the pulmonary artery, and through collateral vessels. Consequently, the

measurement of total pulmonary artery and capillary flows permitted the determination of the volume flow through the collateral circulation to the lung by the following formula:

$$9. \text{Collateral circulation to the lungs (ml. per minute)} = \text{pulmonary capillary flow (ml. per minute)} - \text{pulmonary artery flow (ml. per minute)}$$

It has been impossible, with the methods described, to state whether or not the collateral circulation consists of a patent ductus or of a series of vessels originating in the aorta. Consequently, the sum total of the blood flowing to the lung through channels other than the pulmonary artery will be referred to as "collateral circulation" in the succeeding papers.

In cases of tetralogy of Fallot systemic flow exceeded that through the pulmonary artery, the difference between the two volume flows representing the shunt from the right ventricle through the interventricular septal defect or the overriding aorta. Therefore, it was possible to calculate the intracardiac shunt, "right to left.":

$$\text{Formula 10: Intracardiac shunt (right to left) (ml. per minute)} = \text{volume of blood flow through the systemic circulation (ml. per minute)} - \text{volume of blood flow through pulmonary artery (ml. per minute)}$$

Calculation of mixed venous pulmonary flow: It became evident that the volume of intracardiac right to left shunt rather than a decrease in pulmonary blood flow contributed to arterial unsaturation by preventing the contact of mixed venous blood with pulmonary epithelium. Formulae were therefore derived which permitted calculations of the amount of mixed venous blood perfusing the lung. Mixed venous pulmonary flow may be defined as the volume of blood which after its return to the right auricle, ultimately reaches the pulmonary alveoli. Since it is the only component of the circulating blood which becomes effectively oxygenated in the alveolar space it will be referred to as the "effective pulmonary blood flow".

$$11. \text{Effective pulmonary blood flow (ml. per minute)}$$

$$= \frac{\text{O}_2 \text{ consumption (ml. per min.)}}{\text{O}_2 \text{ content of pulmonary vein blood (vol. per cent)} - \text{O}_2 \text{ content of right auricle blood (vol. per cent)}} \times 100$$

12. Effective pulmonary blood flow (ml. per min.)

$$= \frac{\text{CO}_2 \text{ output (ml. per min.)}}{\text{CO}_2 \text{ content of right auricle (vol. per cent)} - \text{CO}_2 \text{ content of pulmonary vein (vol. per cent)}} \times 100$$

The percentage of the total mixed venous blood which reaches the pulmonary epithelium was subsequently calculated with the following equation.

13. Percentage of total mixed venous blood reaching lung

$$= \frac{\text{effective pulmonary blood flow}}{\text{systemic blood flow}} \times 100$$

The relationship between pulmonary ventilation and gas exchange at rest and during exercise: The relationship between the breathing requirements (volume ventilation per minute) and the oxygen consumption and carbon dioxide production were investigated at rest and during a standard exercise identical with that described by Cournand and Richards (10). In several instances the breathing requirements were also studied during the period of recovery from exercise. The air expired during exercise was collected in a Douglas bag and its oxygen and carbon dioxide contents as well as its total volume were subsequently determined. Changes in minute volume during the recovery were recorded on an electrically driven kymograph which was connected with the bell of a Tissot spirometer. Arterial blood samples were taken preceding and immediately following the performance of the exercise.

Special techniques: Arterial and intracardiac pressures were optically recorded by means of a Hamilton manometer (11). Membranes of various sensitivities were used. Systemic mean pressures in the femoral artery were calculated by planimetric integration of the area under the pressure curve. The resistance in the systemic circulation (peripheral resistance) was calculated by the formula of Aperia (12):

14. Peripheral resistance

$$= \frac{\text{mean systemic blood pressure}}{\text{flow in systemic circulation per second}} \times 1332$$

This formula represents the loss of pressure head in the peripheral circulation in absolute units, one unit representing one dyne /sec/cm⁵.

The method of Haldane and Priestley was followed in collecting alveolar air samples (13). This procedure required a degree of cooperation from the subject which could not be obtained from younger children. In these individuals an automatic alveolar air sampler, first described by Smith and Heinbecker, was employed (14). Alveolar samples obtained with the automatic sampler agreed with those obtained by the method of Haldane and Priestley.

Carbon dioxide dissociation curves were constructed for the blood of each individual since the slope of the curve varied with the hemoglobin content of his blood. The method described by Peters was followed, the carbon dioxide contents and tensions being plotted against their logarithms (15). By following this procedure, linear oxygenated absorption curves were obtained from the points determined by equilibration of 5 cc. samples of blood with carbon dioxide concentrations of 4 and 7 per cent respectively, the remaining volume being composed of oxygen. Equilibration was carried out in a water bath at a temperature of 37°C. in tonometers of 450 cc. capacity.

All tests were performed under basal conditions without anesthesia. Carbon dioxide eliminated and oxygen consumed were determined by analysis of expired air collected in a Douglas bag, and measured in a Tissot spirometer. The gas analysis apparatus of Haldane, Boothby and Sandiford was used for the measurements of oxygen and carbon dioxide (16). All gas volumes were expressed in terms of dry gas at 760 mm. mercury and at 0 degrees Centigrade.

Arterial blood was obtained by puncture of the brachial or femoral artery, after infiltration of the skin with 2 per cent procaine hydrochloride. The blood was collected under oil in syringes, each containing 2 mgs. sodium fluoride and 15 mgs. potassium oxalate per 10 cc. of blood. The oxygen capacity was determined by equilibration of 6 to 8 cc. of blood with room air for 20 minutes in tonometers of 450 cc. capacity. All blood gas analyses were carried out in the manometric apparatus of Van Slyke (17).

DISCUSSION

The preceding description of methods demonstrates the difficulties encountered in adapting the Fick principle to the study of the cir-

culatation in individuals with malformations of the heart. This becomes especially apparent in the determination of the blood flow through the pulmonary artery. Interventricular admixture of venous with oxygenated blood results in concentrations of carbon dioxide and oxygen in the femoral artery which differ from those in the pulmonary vein. The tensions of these gases in the pulmonary vein, therefore, have to be calculated indirectly. The carbon dioxide content of the pulmonary vein is derived from the alveolar carbon dioxide tension, the oxygen content by multiplying the oxygen capacity of the blood by an assumed pulmonary vein saturation of 95 per cent. Results to be described in detail in subsequent publications confirm the validity of the latter assumption.

The failure to secure blood samples from the pulmonary artery of patients with severe pulmonary stenosis introduces a serious obstacle to the calculation of pulmonary artery blood flow. In these cases values for right ventricular blood must be substituted for those of the pulmonary artery, although in hearts with large interventricular shunts the gaseous content of right ventricular blood differs from that of the pulmonary artery. On the other hand, results, obtained in several cases with moderate stenosis in which the pulmonary artery could be intubated, demonstrate that the oxygen and carbon dioxide contents of the right ventricle and of the pulmonary artery differ only slightly if the catheter tip lies close to the pulmonary valve.

The development of a large collateral circulation to the lungs adds to the difficulties already encountered in the estimation of pulmonary artery blood flow. In these the quantity of oxygen consumed or of carbon dioxide released is too high in relation to the total minute volume perfusing the pulmonary artery. With an increase in the ratio of collateral circulation to pulmonary artery flow the accuracy of the formulae 4 and 5 diminishes. Consequently establishing the diagnosis of pulmonary atresia, in which pulmonary artery flow is zero, is impossible by these methods.

The foregoing discussion makes it apparent that values calculated for blood flow through the pulmonary artery can only be considered approximations. On the other hand, the values are sufficiently reliable to permit their use in the preoperative recognition of pulmonary stenosis. This is demonstrated by the fact that in all instances in

which evidence for reduced pulmonary artery flow was obtained by calculation, pulmonary stenosis was found during operation.

In contrast to the determination of pulmonary artery flow, the total amount of blood perfusing the lung (pulmonary capillary flow) can be calculated by indirect means only. One of the advantages of the indirect method lies in the fact that by comparing the results therefrom with those of catheterization of the pulmonary artery or right ventricle, the amount of collateral circulation to the lung can be estimated. This is of diagnostic importance since it is often difficult to distinguish on clinical or fluoroscopic grounds increased collateral circulation from increased pulmonary artery flow, which is found in Eisenmenger's syndrome. Furthermore, the amount of collateral circulation is of physiological importance as it represents one of the mechanisms by which the individual adapts to decreased pulmonary artery blood flow. Finally, following the Blalock operation, the determination of pulmonary capillary flow is of aid in the calculation of postoperative changes in the circulating volume of pulmonary blood.

The most important error in this method lies in a possible recirculation of carbon dioxide through the lung during equilibration a factor which results in abnormally high carbon dioxide values for blood entering the pulmonary capillaries and correspondingly low figures for pulmonary capillary flow (9).

The determination of the volume of mixed venous pulmonary flow is of importance since it is the only component of the circulating blood which becomes effectively oxygenated in the pulmonary alveoli. Consequently this component is the "effective pulmonary blood flow," and determines the peripheral arterial oxygen saturation. Furthermore, postoperatively, the effect of the Blalock-Taussig operation can be calculated quantitatively by changes in the effective pulmonary flow.

Studies comparing the relationship of pulmonary ventilation and gas exchange during rest and exercise are undertaken primarily to investigate the ability of the individual to adjust his pulmonary flow to the increased respiratory demands of exercise. It has been shown that in normal individuals, the ratio of oxygen intake to the ventilatory volume rises during exercise, while the ratio of carbon dioxide output to liters of ventilation remains constant (10). In

individuals, however, in whom large areas of the lung during exercise are ventilated but not perfused, the ratio of oxygen consumption to respiratory volume decreases. If the circulation through the lung is very seriously impaired, then the ratio of carbon dioxide output to liters of ventilation also declines.

Analyses for respiratory gases in arterial blood at rest and during exercise have a similar purpose (10). In normal subjects a standard exercise is immediately followed by a slight decline in the oxygen saturation of arterial blood and an appreciable drop in carbon dioxide content. During exercise, when shunting of blood occurs by passage through vessels which fail to reach the alveolar epithelium, the arterial oxygen saturation decreases and the carbon dioxide content of arterial blood usually rises. Therefore, in the recognition and physiological interpretation of variations in the effective pulmonary blood flow, the exercise test represents a valuable supplement to the methods already described.

SUMMARY

Technical procedures employed in the study of congenital heart diseases belonging to the cyanotic group, have been described.

The physiological and diagnostic values of these procedures and their limitations are discussed.

We are indebted to Mrs. F. Kelmenson, Miss E. Keavney, Miss B. Harris and Mrs. J. Morse for their cooperation and assistance.

REFERENCES

1. BLALOCK, A., AND TAUSSIG, H. B., Surgical treatment of malformations of the heart in which there is pulmonary stenosis or pulmonary atresia, J. A. M. A. 128: 189, 1945.
2. FICK, A., Ueber die Messung des Blutquantums in den Herzventrikeln, Sitzung. phys. med. Gesell. zu Würzburg, Jul. 1870, p. 16.
- 3a. Cournand, A., Measurement of cardiac output in man using right heart catheterization; description of technique, discussion of validity and of place in study of circulation, Federation Proc. 4: 207, 1945.
- 3b. Cournand, A., Personal communication.
4. COMROE, J. H., JR., AND DRIPPS, R. D., JR., The oxygen tension of arterial blood and alveolar air in normal human subjects, Am. J. Physiol. 142: 700, 1944.
5. DEXTER, L., Personal communication.

6. WARREN, J. V., STEAD, E. A., JR. AND BRANNON, E. S., The Cardiac Output in Man: A Study of some of the Errors in the Method of Right Heart Catheterization, *Am. J. Physiol.* **145**: No. 4, 458, 1946.
7. CHRISTIANSEN, J., DOUGLAS, C. G., AND HALDANE, J. S., Absorption and dissociation of carbon dioxide by human blood, *J. Physiol.* **48**: 244, 1914.
8. FIELD, H., BOCK, A. V., GILDEA, E. F., AND LATHROP, F. L., The rate of the circulation of the blood in normal resting individuals, *J. Clin. Investigation* **1**: 65, 1924.
9. HAMILTON, W. F., Notes on the development of the physiology of cardiac output, *Federation Proc.* **4**: 183, 1945.
10. COURNAND, A., AND RICHARDS, D. W., JR., Pulmonary insufficiency. Discussion of the physiological classification and presentation of clinical tests, *Am. Rev. Tuberc.* **44**: 26, 1941.
11. HAMILTON, W. F., BREWER, G., AND BROTMAN, I. Pressure pulse contours in the intact animal. Analytical description of a new high-frequency hypodermic manometer with illustrative curves of simultaneous arterial and intracardiac pressures. *Am. J. Physiol.* **107**: 427, 1934.
12. APERIA, A., Hemodynamic studies, *Skandinav. Arch. f. Physiol.*, Supplement 16 (to vol. 83), 1940.
13. HALDANE, J. S., AND PRIESTLEY, J. G., The regulation of the lung-ventilation, *J. Physiol.* **32**: 225, 1905.
14. SMITH, R. G., AND HEINBECKER, P., A method of obtaining alveolar air from normal dogs and a comparison of the carbon dioxide tensions of alveolar air and arterial blood, *Am. J. Physiol.* **84**: 271, 1928.
15. PETERS, J. P., BULGER, H. A., AND EISEMAN, A. J., Studies on the carbon dioxide absorption curve of human blood. II. The nature of the curve representing the relation of pH to BHCO_3 , *J. Biol. Chem.* **55**: 709, 1923.
16. HALDANE, J. S., *Methods of Air analysis.* London, Charles Griffin and Co., Ltd., 1912.
17. VAN SLYKE, D. D., AND NEILL, J. M., The Determination of Gases in Blood and Other Solutions by Vacuum Extraction and by Manometric Measurement, *J. Biol. Chem.* **61**: 523, 1924.

PHYSIOLOGICAL STUDIES IN CONGENITAL HEART DISEASE*

II. RESULTS OF PREOPERATIVE STUDIES IN PATIENTS WITH TETRALOGY OF FALLOT

R. J. BING, L. D. VANDAM, AND F. D. GRAY, JR.

From the Departments of Surgery and Pediatrics, The Johns Hopkins University and Hospital

In the first paper of this series the various physiological procedures employed in the investigation of congenital heart disease with cyanosis were described (1). This report deals with the results of preoperative studies on patients in whom clinical and physiological examinations indicated the presence of reduced pulmonary blood flow.

The Blood Flow Through the Pulmonary Artery, the Systemic Circulation, and the Volume of Intracardiac Shunt: The volume of blood flowing through the pulmonary arteries was calculated according to formula 5 of the preceding paper in a total series of 120 patients with pulmonic stenosis. Table I illustrates that in 36 of 48 consecutive studies selected for presentation in this paper the flow through the pulmonary artery per square meter of body surface was below 3.00 liters per minute which is the normal cardiac index established by Cournand and associates (2). The systemic blood flow, on the other hand, calculated per square meter of body surface according to formula 6 of the preceding paper, showed marked variations above and below the values for normal cardiac index. In 14 patients the rate of flow in the systemic circulation was increased above normal standards. As a result of the increased rate of flow through the peripheral circulation the differences between the oxygen and carbon dioxide contents of peripheral arterial and right auricular bloods were below normal. In 9 individuals the systemic blood flow approximated Cournand's standards for cardiac index, whereas in 13 the systemic flow was below these standards (Table I). In one individual the calculated blood flow through the pulmonary artery was 20 per cent of normal (case # 12, Table I). Although a preoperative diagnosis of pulmonary atresia could not be

* This work was supported by a grant from the Commonwealth Fund.

made for reasons outlined in the preceding paper (1), the extremely low values for pulmonary artery flow suggested the presence of this condition. This assumption was confirmed at operation.

A comparison of the data obtained for systemic flows with those for the pulmonary artery demonstrated that the former exceeded pulmonary artery flow by from 0 to 9.7 liters per minute. This indi-

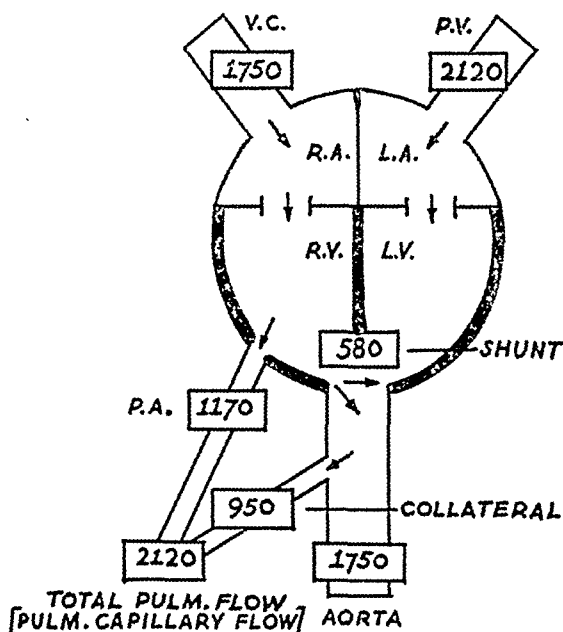


FIG. 1. illustrates the results obtained in a case (E. R. age 17) of tetralogy of Fallot. It may be seen that the systemic flow exceeds that through the pulmonary artery, resulting in a right to left shunt of 580 cc./minute. The pulmonary capillary flow exceeds that through the pulmonary artery, indicating the presence of collateral circulation to the lung of 950 cc./minute.

cated that in tetralogy of Fallot some of the returning mixed venous blood, unable to pass through the stenosed pulmonary artery into the lung, coursed through the interventricular septal defect and the overriding aorta directly into the systemic circulation. Consequently, as illustrated in Fig. 1, which represents a typical case of tetralogy of Fallot, the overall direction of the intracardiac shunt was from right to left. However, there was some concomitant flow from left to right

through the septal defect. This was indicated by the observation that the oxygen content of right ventricular blood exceeded that of the right auricle in the majority of cases (Table I). In 2 individuals (#19 and 34, Table I) both systemic and pulmonary artery flows were reduced below normal values for cardiac index by an equal amount. It could be assumed that in these cases of pulmonic stenosis the accompanying interventricular septal defect was small and the aorta arose chiefly from the left ventricle. This assumption was supported by the fact that the oxygen saturation of peripheral arterial blood in these patients was above 88 per cent despite greatly reduced flow through the pulmonary artery (Table I). These considerations suggested that the variations in systemic flow observed in patients with tetralogy of Fallot were related to the degree of pulmonary stenosis and the size of the intracardiac shunt.

The Pulmonary Capillary Flow (Total Pulmonary Flow): Values for pulmonary capillary flow, calculated according to formula 8 of the preceding paper, are listed in Table II. In most of the younger individuals the values obtained with this method agreed closely with those determined for pulmonary artery flow. In the majority of older patients, however, pulmonary capillary flow exceeded pulmonary artery flow, indicating that the lungs received blood from sources other than the pulmonary artery (Fig. 1). Direct observations of collateral circulation during operation have confirmed these findings (3). A linear relationship, however, between age and the magnitude of collateral circulation has not been obtained. This should be expected since in younger individuals atresia of the pulmonary artery required sufficient collateral circulation for the survival of the individual. A large calculated difference between pulmonary capillary and pulmonary artery flow was found in the oldest person of this series (#6, Table II), who had been clinically classified as a case of Eisenmenger's syndrome. At operation the pleural cavity was found obliterated by adhesions through which innumerable collaterals from intercostal and mammary arteries passed to the lung. In other patients in whom calculations indicated the presence of extensive collateral circulation to the lungs large bronchial and multiple accessory arteries were found. It seemed probable that the collateral circulation to the lung represented an important factor in the physiological adjustments of these individuals to their abnormally low pulmonary artery flow.

TABLE I

Data Obtained by Right Heart Catheterization

NO.	DATE 1946	SUBJ.	AGE	SEX	SURF. AREA M ²	CC. O ₂ CONS. per min.	CC. CO ₂ PROD. per min.	CC. CO ₂ CALC. per min.	R.Q.	MIN. VOL. L/M	B.M.R.	R.V.		P. A.		R. A.		P. V.		F. A.		O ₂ CAP. VOL. %	O ₂ SAT. %	CARDIAC OUTPUT LITERS/MIN./M ²		RIGHT TO LEFT INTRA- CARD. SHUNT LITERS Min./M ²	NO.
												O ₂ Vol. %	CO ₂ Vol. %	O ₂ Vol. %	CO ₂ Vol. %	O ₂ Vol. %	CO ₂ Vol. %	O ₂ Vol. %	CO ₂ Vol. %	O ₂ Vol. %	CO ₂ Vol. %			Pulm.	Syst.		
1	3/12	V. S.	25	M	1.68	241	218		.89	9.7	+9	21.3	35.8	18.8	35.3	32.4	32.4	22.5	31.7	34.0	60.6			1.29	3.87	2.57	1
2	3/18	C. H.	15	M	1.6	195	153		.79	6.22	-9	22.	32.4	18.2	36.3	31.3*	25.6*	22.9	33.2	32.5	71.			1.2	2.58	1.38	2
3	3/21	D. M.	10	M	.83	95	85		.87	3.01	-32	18.9	38.1	18.2	41.7	27.3	29.0	22.7	37.3	28.5	79.8			1.37	2.55	1.1	3
4	3/26	D. S.	18	F	1.3	138	117		.83	4.43	-18	18.7	35.6	17.6	37.7	30.4	24.0	20.4	35.7	32.0	63.8			.89	3.7	2.8	4
5	4/17	O. J.	24	M	1.8	162	152		.9	4.5	-30	23.0	44.7	20.4	46.3	30.8	36.0	24.0	43.0	32.0	75.0			1.16	2.52	1.36	5
6	4/23	M. C.	15	F	1.28	161	143		.88	5.25	-5	21.3	37.3	22.8		33.8	29.0	24.3	32.5	35.3	69.0			1.08	8.4	7.5	6
7	4/30	L. S.	26	M	1.68	172	153		.88	5.11	-23	20.2	39.2	22.3	38.2	32.2	32.8	24.4	36.1	34.1	71.5			.85	4.8	4.04	7
8	5/10	J. A. C.	9	F	.98	130	144	110	1.1	7.03	-19	17.2	37.2	14.3	40.8	24.8*	30.8*	17.7	36.4	26.3	67.5			1.05	3.84	2.79	8
9	5/14	T. M.	7	M	.85	132	152	107	1.12	6.84	-15	24.7	31.5	21.9	35.6	31.5	24.9			33.0	65.0			2.03			9
10	5/17	C. H.	21	F	1.43	119	119		1.0	4.5	-34	16.0	40.9	14.6	42.2	25.	30.5	16.0	39.5	26.3	60.8			.93	5.89	4.9	10
11	5/21	R. A.	22	M	1.46	156	157		1.0	6.9	-25	26.7	22.3	23.1	26.4	33.5	22.4	28.9	20.7	35.2	82.0			1.58	1.84	.26	11
12	5/28	G. S.	19	F	1.5	103	113	84	1.08	4.07	-48	19.5	41.8	16.9	45.1	29.9	30.0	24.5	37.6	31.5	77.7			.66	.90	.24	12
13	5/31	R. C.	16	M	1.35	162	207	132	1.26	8.2	-24	18.5	39.3	18.3	40.1	30.4	32.0	22.8	34.9	31.7	72.2			1.01	2.64	1.6	13
14	6/6	A. P.	18	F	1.3	131	109		.82	4.82	-23	11.7	40.3	13.7	40.0	20.0	34.4	18.1	35.8	21.0	85.5			1.18	2.24	1.06	14
15	6/12	L. P.	20	F	1.59	164	134		.81	5.2	-19	19.3	36.0	19.8	35.8	28.8	30.0	24.2	29.4	30.3	79.9			1.08	2.38	1.29	15
16	6/19	J. H.	17	M	1.54	177	147		.82	8.6	-27	22.5	31.2	20.1	34.5	37.7	23.0	22.8	29.8	39.8	57.4			.75	4.2	3.48	16
17	6/26	A. F.	7	M	.66	126	115		.90	6.3	-8	17.3	35.3	17.5	34.3	33.1	24.4	19.9	31.6	34.5	57.8			1.22	8.2	6.9	17
18	7/3	J. O.	18	M	1.68	180	153		.73	4.1	-27	23.8	45.2	22.9	43.6	31.7	38.0	26.6	40.0	33.4	80.0			1.37	2.97	1.6	18
19	7/9	V. H.	5	M	.76	105	91		.83	4.68	-26	12.0	38.3	9.6	37.4	19.0	24.2	17.8	38.8	20.0	89.0			1.98	1.9	0	19
20	7/11	D. F.	12	M	1.34	150	165	122	1.08	6.79	-33	16.9	40.6	16.5	44.4	23.1	35.5	19.4	37.8	24.3	80.1			1.8	3.9	2.0	20
21	7/17	J. F.	8	F	.95	77	72		.90	3.2	-48	17.4	42.9	16.3	41.4	29.8	33.0	20.9	36.1	31.5	66.0			.65	1.75	1.0	21
22	7/23	J. F.	16	M	1.7	211	241	171	1.1	7.9	-23	14.1	40.7	12.5	41.8	25.4	33.2	21.0	39.8	26.7	78.6			.9	1.5	.5	22
23	7/26	E. R.	17	F	1.43	112	122	91	1.08	4.9	-39	17.8	38.5	18.1	38.2	27.6	36.5	24.6	39.5	29.1	84.5			.8	1.23	.4	23

24	8/6	B. H.	8	F	.96	111	132	90	1.18	7.17	-28	14.3	42.0				14.8	42.5	22.2	32.3	17.1	37.6	23.3	73.4	1.47	5.16	3.67
25	9/4	D. B.	7	M	.77	95	97	77	1.02	5.8	-24	14.2	34.3				12.1	34.5	28.8	18.7	17.9	29.7	30.4	58.6	.8	2.1	1.2
26	9/5	V. B.	14	F	1.01	123	107		.87	6.28	-24	16.7	39.7	16.3	38.5		15.2	40.2	26.7	29.1	21.1	35.0	28.2	75.0	1.17	1.25	.87
27	9/11	C. P.	11	M	1.21	132	117		.89	7.02	-31	18.9	36.7	21.1	35.8		20.2	35.1	31.1	27.7			32.7	55.0	1.09		
28	9/18	R. W.	18	M	1.5	195	231	159	1.18	11.8	-15	24.8	35.0				20.5	39.6	31.4	29.6	26.8	31.	33.0	81.0	1.97	2.06	.08
29	9/21	R. F.	10	F	1.02	161	142		.88	8.0	-1	26.8	36.5	24.8	38.2		19.3	14.9	32.5	28.9	24.2	39.4	34.0	70.9	2.06	3.24	1.18
30	10/4	J. McM.	10	M	1.14	153	166	124	1.09	7.95	-4	13.8	39.4				12.8	41.4	22.2	34.5	14.4	40.9	24.5	58.5	1.61	8.5	6.78
31	10/15	J. M.	5	F	.82	91	90		.98	4.15	-38	16.9	41.0	16.7	40.2		18.3	44.7	23.4	32.8	19.3	41.7	24.7	78.0	1.64	11.4	9.7
32	10/21	A. S.	21	F	1.59	148	131		.89	6.2	-26	14.25	41.7				13.7	40.2	22.9	36.8	18.0	35.4	24.1	74.8	1.07	2.18	1.11
33	10/29	A. O. C.	12	M	.93	96	80		.83	4.15	-41	17.3	38.7				17.0	38.0	29.1	24.6	19.6	35.0	30.4	64.5	.92	3.3	2.39
34	11/8	S. C.	14	M	1.5	135	140	109	1.03	6.9	-46	18.7	38.2	18.8	37.		17.1	39.8	24.4	31.2	23.1	34.0	25.5	91.0	1.6	1.5	
35	11/11	A. deH.	9	F	.9	102	125	83	1.23	4.82	-30	20.2	41.5				18.3	44.9	26.6	35.2			28.0	61.8	1.48		
36	11/14	E. L.	20	F	1.44	215	220	172	1.01	7.35	+18	19.5	38.8				19.1	38.2	26.3	30.2	22.6	35.0	27.7	82.5	2.2	4.2	2.06

• Direct determination

Of further interest were 4 cases in which the clinical findings indicated the presence of a patent ductus arteriosus together with reduced pulmonary artery flow (#4, 9, 19, 20, Table II). Figure 2, which presents the findings in one of these cases, demonstrates that the pulmonary capillary flow exceeded the flow through the pulmonary artery, because of a large collateral circulation to the lung contributed by the

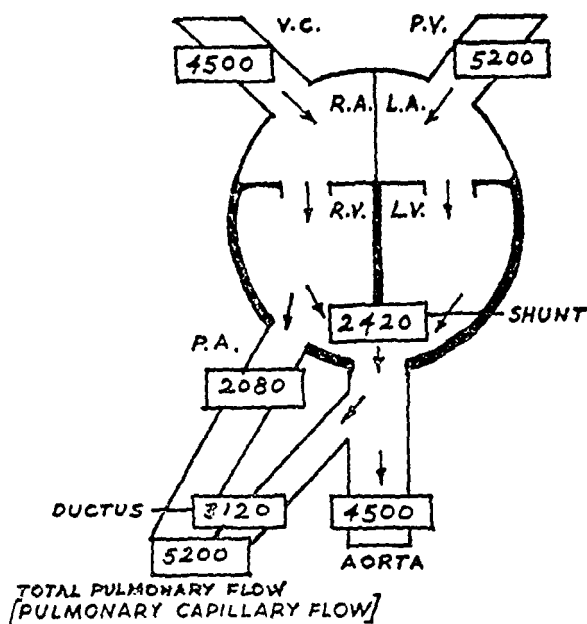


FIG. 2. represents the volume flows in a patient O. J. age 24 with tetralogy of Fallot and patent ductus arteriosus. The intracardiac right to left shunt is 2420 cc./minute. The volume flow in the ductus, calculated as the difference between pulmonary capillary and pulmonary artery flows, is 3120 cc./minute.

ductus. Confirmatory evidence for the existence of a patent ductus arteriosus in the presence of pulmonary stenosis has not been obtained in these individuals since operation has not been performed. However, the combination of clinical and physiological data strongly suggested the combination of a patent ductus and pulmonary stenosis.

Blood Pressures and Peripheral Resistance: Intracardiac and systemic blood pressures were obtained in a series of 22 patients with clinical

and physiological evidence of tetralogy of Fallot. Table III shows that the right intraventricular systolic pressure was elevated in every instance except one (# 21, Table III); pressures recorded ranged from 20 to 110 mm. above the normal values of 18 to 28 mm. of mercury. The diastolic pressure in the right ventricle was elevated in 8 cases (Table III). It is probable that in several individuals the high diastolic pressures were the result of backward failure which was clinically manifest in these individuals. In 6 cases where the catheter was passed into the pulmonary artery through the stenosis, a sharp fall in pressure was observed (Fig. 3). In some of these individuals the pulmonary artery pressures were so low that only the slightest excursions are recorded. It seemed of special interest that in a large number of cases systolic pressures in the femoral artery were of the same order as those in the right ventricle (Table III), although the pressures were not recorded simultaneously. Complete agreement in the heights of the systolic pressures existing in the right ventricle and the aorta was obtained in 3 subjects in whom the catheter was passed from the right ventricle through the aortic valve (Fig. 4) indicating equilibration of pressures in the two chambers.

In 19 cases the peripheral resistance was calculated according to the formula of Aperia, which mathematically expresses the ratio between pressure and resistance (4). Table III shows that values obtained for peripheral resistance ranged from 600 to 6000 dynes/sec/cm²/M²., while the blood pressures remained approximately constant. Consequently a logarithmic relationship existed between systemic flow and peripheral resistance (Fig. 5). Since the results reported in the preceding paragraphs indicated that the variations in systemic flow were related to the size of the intracardiac shunt, it would appear that changes in the peripheral resistance occurred as a compensatory response to the alterations in flow.

Oxygen Consumption and Basal Metabolic Rate: Table I demonstrates that the oxygen consumption in the great majority of individuals with decreased effective pulmonary flow was reduced. A similar observation has been made by Dexter (5). The basal metabolic rate calculated from these figures ranged as low as -48. This finding was of considerable interest since it suggested that the decrease in the overall metabolic processes might be the result of prolonged anoxemia.

TABLE II

Data Obtained by the Equilibration Method for the Determination of Pulmonary Capillary Flow

NO.	DATE 1946	SUBJ.	SEX	AGE	SURF. AREA M ²	CC. CO ₂ PROD. per min.	CC. CO ₂ CALC. per min.	R.Q.	M.V.L./M	CO ₂ INCOMING CAP. BLOOD			CO ₂ OUTGOING BLOOD			LITERS TOTAL PULM. FLOW/M ²	CC. COLLAT. PULM. FLOW/M ²	NO.
										%	Tension mm. Hg.	Vol. %	%	Tension mm. Hg.	Vol. %			
1	3/13	C.H.	M	15	1.6	215	147	1.18	7.64	5.14	36.4	31.0	3.18	22.5	23.0	1.1	0	1
2	3/18	D.M.	M	10	.83	123		1.0	4.17	5.35	38.2	37.5	3.09	22.0	26.6	1.3	0	2
3	3/27	D.S.	F	18	1.32	117		.83	4.45	4.40	31.5	31.0	3.50	25.0	25.0	1.5	574	3
4	4/16	O.J.	M	24	1.78	172		.96	4.5	4.8	34.7	39.1	4.17	29.8	35.8	2.9	1752	4
5	4/22	M.C.	F	15	1.28	162.5		.93	6.44	4.38	31.3	33.0	2.76	19.8	25.7	1.7	720	5
6	4/29	L.S.	M	26	1.25	237	162	1.18	5.88	4.86	34.8	38.8	3.75	26.9	32.6	2.0	1132	6
7	5/8	J.A.C.	F	9½	.98	108.7		.93	4.81	4.98	35.3	35.3	2.68	19.0	24.5	1.0	0	7
8	5/13	T.M.	M	7½	.85	137.7	93.9	1.18	6.33	4.17	29.8	31.5	2.76	19.0	24.9	1.7	0	8
9	5/16	C.H.	F	21	1.43	118		.96	4.8	4.48	31.9	36.8	3.52	25.3	32.8	2.5	1518	9
10	5/22	R.A.	M	22	1.46	157.5		1.62	6.93	3.94	28.0	27.2	2.8	20.1	22.4	2.2	643	10
11	5/24	A.P.	F	18	1.3	113.2		.93	5.01	4.69	33.75	38.8	3.80	27.3	35.0	2.3	1065	11
12	5/29	G.S.	F	19	1.5	144	99.6	1.15	5.0	4.97	35.5	37.3	3.5	25.4	31.0	1.2	515	12
13	6/3	R.C.	M	16	1.35	206	131.7	1.26	8.2	4.5	32.0	36.2	3.35	23.8	31.5	2.1	1060	13
14	6/5	S.E.	M	19	1.7	159	119	1.07	6.75	4.95	35.3	41.7	4.07	24.1	38.2	2.0	0	14
15	6/11	L.P.	F	20	1.59	134		.81	5.2	4.51	32.4	34.4	3.39	24.2	28.8	1.5	423	15
16	6/12	V.H.	M	5	.76	90.8		.83	4.7	3.76	26.8	29.8	2.62	18.68	24.2	2.2	170	16
17	6/19	J.H.	M	17	1.54	147		.82	8.6	4.2	30.3	29.2	2.9	20.6	24.0	1.8	1083	17
18	6/29	J.O.	M	18	1.68	153		.86	4.7	5.1	36.5	41.1	4.3	31.2	38.0	2.9	1575	18
19	7/10	D.F.	M	12	1.34	179.6	117.8	1.2	6.6	4.3	30.0	37.2	3.8	27.1	35.1	4.2	2361	19
20	7/16	J.F.	F	8	.99	73.1		.9	3.5	3.9	28.0	35.2	3.2	23.6	32.6	3.0	2310	20
21	7/22	J.F.	M	16	1.70	241	171	1.1	7.9	4.8	34.2	36.8	4.4	31.3	34.2	3.8	2790	21
22	7/29	E.R.	F	17	1.43	121	91	1.08	4.9	5.03	36.0	40.8	4.1	29.4	36.6	1.5	660	22
23	8/5	B.H.	F	8	.96	98	69	1.15	5.9	4.8	34.3	39.7	3.4	24.0	32.0	9.4		23
24	9/4	V.B.	F	14	1.01	88.3		.71	4.5	4.5	32.7	34.5	3.4	24.8	29.1	1.6	445	24

25	9/7	D. B.	M	7	.77	97	76	1.02	5.8	3.9	28.0	26.0	2.3	16.7	18.7	1.4	524	25
26	9/10	C. P.	M	11	1.21	93		.91	6.4	4.05	28.9	31.0	3.4	24.1	27.7	2.4	1260	26
27	9/12	W. B.	M	15	.91	77.8		.88	5.5	3.26	23.4	27.8	2.19	15.7	23.2	1.9		27
28	9/13	A. S.	M	25	1.62	193.5	146.5	1.06	6.84	4.9	36.0	40.0	4.5	32.2	37.0	3.0	990	28
29	9/17	R. W.	M	18	1.5	231	156	1.18	11.8	4.03	29.0	32.0	3.39	24.4	29.6	2.98	1480	29
30	9/20	R. F.	F	10	1.2	108		.96	5.21	4.14	29.5	31.3	3.5	24.6	28.3	3.5	1480	30
31	9/23	F. C.	F	14	1.22	138	97	1.5	8.9	3.25	23.2	26.2	2.6	19.8	23.5	2.9		31
32	10/1	J. M.	M	10	1.14	166	123.5	1.09	7.95	4.78	34.1	38.0	3.84	27.4	34.5	2.3	710	32
33	10/12	J. M.	F	5	.82	89.7		.98	4.15	4.59	32.7	37.6	3.64	25.7	32.8	2.3	610	33
34	10/18	A. S.	F	21	1.59	171.5	132	1.07	7.55	5.15	36.2	41.0	3.69	25.9	36.2	1.8	685	34
35	10/28	A. O.	M	12	.93	80		.83	4.15	4.81	34.7	33.8	3.23	23.5	26.6	1.0	150	35
36	11/7	A. D.	F	9	.90	92.0	72.5	1.03	4.97	4.75	33.8	37.4	4.13	29.5	35.2	3.70	1200	36
37	11/7	S. C.	M	14	1.5	198	128.5	1.24	10.6	4.46	31.8	33.9	3.88	27.2	31.2	3.20	1560	37
38	11/13	E. L.	F	20	1.44	127		.92	4.41	4.55	32.5	35.5	3.81	27.2	32.3	3.7	1540	38

Although a similar trend was obtained by Lilienthal and Riley in men during anoxia of short duration (6) and by Ogata in rabbits (7), most observers did not notice a reduction in the oxygen consumption of

TABLE III

Intraventricular and Peripheral Blood Pressures and Calculated Peripheral Resistances

NO.	DATE 1946	SUBJECT	SEX	AGE	PRESSURE FEMORAL ARTERY MM. HG.			PRESSURE RIGHT VENTRICLE MM. HG.		SYSTEM. FLOW LITERS/MIN./M ²	PERIPHERAL RESISTANCE DYNES. SEC./CM ⁵ /M ²	NO.
					Syst.	Diast.	Mean	Syst.	Diast.			
1	8/5	B. H.	F	8	120	75	105	128	0	5.16	1630	1
2	9/3	V. B.	F	13	139	86	98	115	9	1.25	6250	2
3	9/9	D. B.	M	10	92	60	70	111	0	2.10	2660	3
4	9/11	C. P.	M	11	94	60	79	128	16	4.5	1404	4
5	9/16	A. S.	M	24				140	0			5
6	9/20	R. F.	F	10	165	100	118	84	14	3.24	2910	6
7	9/23	J. V.	M	12	115	98	106		0			7
8	9/25	R. W.	M	19	120	94	104		0	2.06	4035	8
9	10/4	J. McM.	M	10	128	70	90	58	19	8.5	846	9
10	10/7	B. A.	F	8	92	80	87		0			10
11	10/11	E. R.*	F	17	145	82	96	65 to 100	0	2.14	3740	11
12	10/14	G. W.	M	26	143	90	106		0	2.58	3300	12
13	10/15	J. M.	F	5½	150	88	98	107	6	11.4	685	13
14	10/21	A. S.	F	21	105	71	82	124	6	2.18	3020	14
15	10/29	A. OC.	M	12	121	92	106	116	15	3.3	2570	15
16	11/8	S. C.	M	14	138	83	100	94	0	1.5	5320	16
17	11/11	A. deH.	F	9	126	69	88	96	0	5.95	1185	17
18	11/14	E. L.	F	20	141	96	111	125	20	4.3	2084	18
19	11/22	B. P.	F	11	148	94	116	132	0	11.4	813	19
20	11/25	R. G.	M	8	92	73	82	109	0	8.5	775	20
21	12/3	A. C.	M	15	112	84	93	20	0	3.1	2380	21
22	12/5	G. T.	M	12	114	95	104	143	23	2.9	2850	22

* Postoperative observation.

individuals or animals after prolonged exposure to low barometric pressure (8). It is conceivable that the difference in the results reported was due to the fact that the anoxia produced under experimental conditions was of considerably shorter duration (6, 7). It also seemed probable that the poor nutritional status observed in many of these patients was at least partially responsible for the decreased oxygen

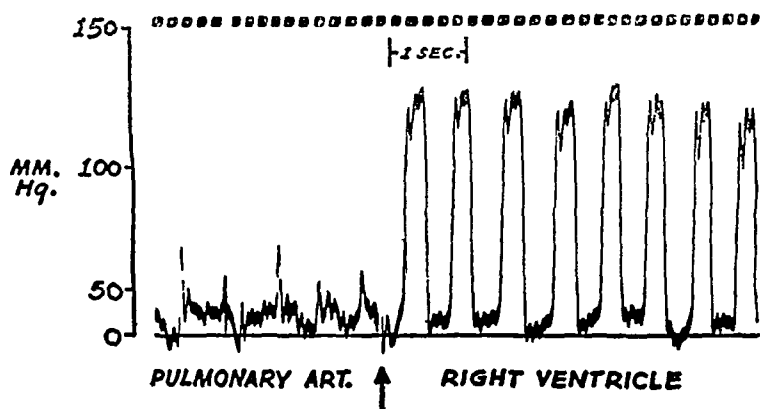


FIG. 3. shows the continuous optical pressure recordings obtained from the pulmonary artery and the right ventricle of a patient G. T. age 12 with tetralogy of Fallot. As the catheter tip was withdrawn from the pulmonary artery into the right ventricle through the semilunar valve (arrow in figure), the systolic pressure rose from 69 to 143 mm. mercury. This demonstrates the presence of pulmonic stenosis. The elevation of the intracardiac diastolic pressure indicates right ventricular strain.

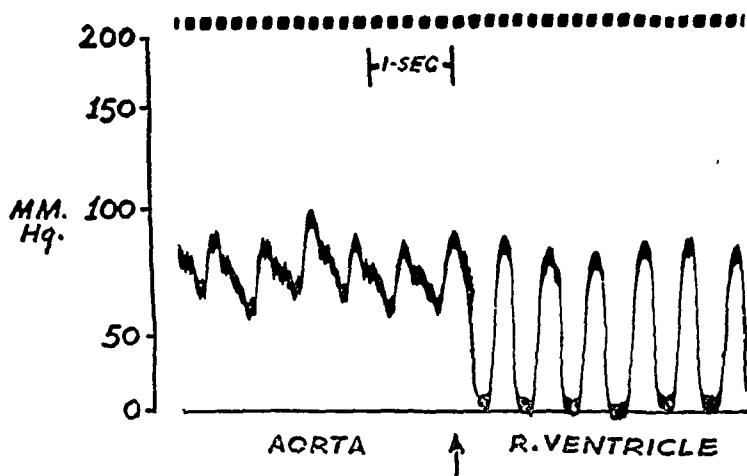


FIG. 4. shows continuous optical recordings obtained from the aorta and the right ventricle of a patient L. P. age 5 with tetralogy of Fallot. Withdrawal of the catheter tip through the aortic valve (arrow in figure) results in a sharp fall of the diastolic pressure, with the systolic pressure remaining constant.

consumption. Findings which will be reported in a subsequent paper demonstrated that the basal metabolic rate of individuals with reduced effective pulmonary blood flow increased considerably following per-

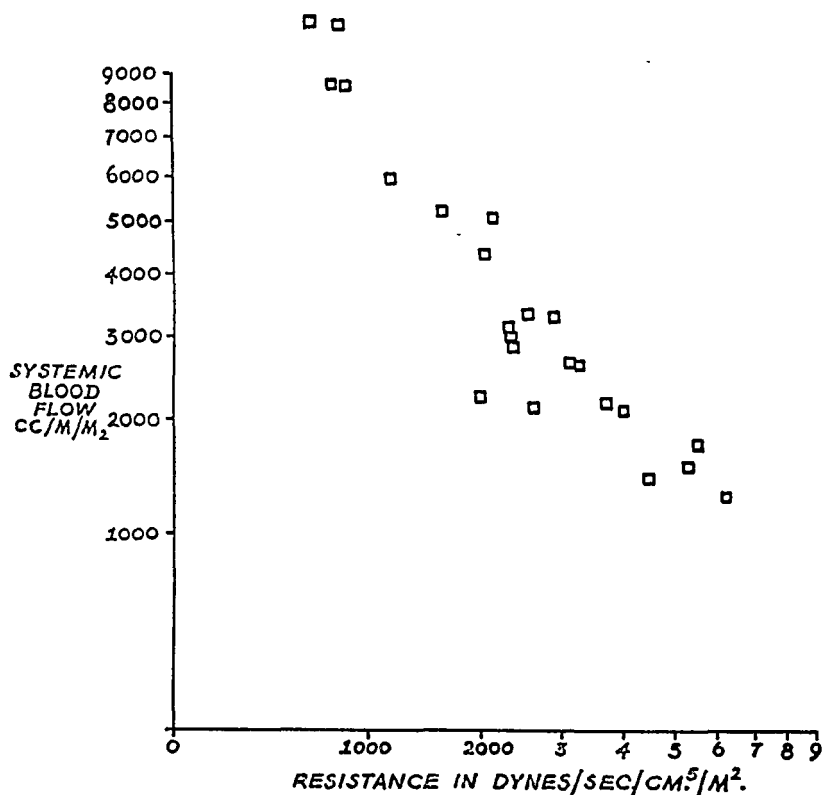


FIG. 5. illustrates the relationship between peripheral resistance and systemic blood flow plotted logarithmically in 23 cases of tetralogy of Fallot. Since the mean pressures remain constant, the variations in systemic flow are responsible for the alterations in the peripheral resistance.

formance of the Blalock-Taussig operation, which raises pulmonary flow.

Results of the Exercise Test: A standard exercise test as described in the preceding paper was performed in a series of 21 patients. As seen in Table IV, in 14 out of 21 cases the ratio of oxygen consumed

per liters of ventilation during exercise fell below its resting value and the carbon dioxide produced per liters of ventilation also declined in 16 individuals. Figure 6 illustrates these results in a typical case of

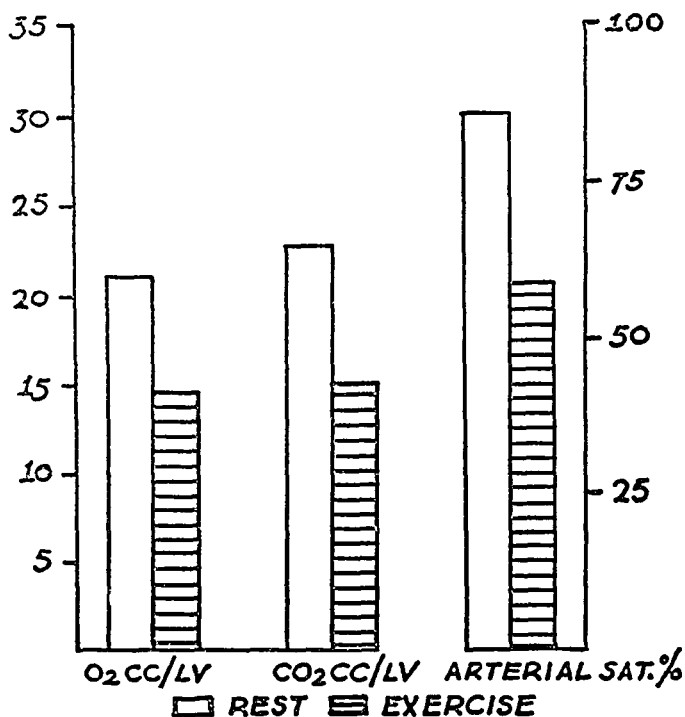


FIG. 6. demonstrates the results of a standard exercise test obtained in a patient E. R. age 17 with tetralogy of Fallot. It can be seen, that in contrast to results obtained in normal individuals, the oxygen consumed and the carbon dioxide produced per liter of ventilation as well as the arterial oxygen saturation declined.

tetralogy of Fallot. This was contrary to observations on normal individuals in whom the standard exercise results in a significant increase in the oxygen and a slight rise in the carbon dioxide ratios (9). This fall in the ratios in individuals with pulmonic stenosis was apparently the result of limited circulating volume of mixed venous blood through the lung during exercise. In contrast to these findings were the results obtained in some individuals who had developed large collateral circu-

lation to the lung. In one of these cases (#2, Table IV) the collateral flow was 1480 cc./M². Data in Table IV demonstrate that in

TABLE IV
Results Obtained with the Standard Exercise Test

NO.	DATE 1946	SUBJ.	AGE	SEX	VENT. LIT./MIN./M ²	CO ₂ CC. M ²	CO ₂ CC. LV	O ₂ CC. M ²	O ₂ CC. LV	R.Q.	ART. O ₂ VOL%	ART. CO ₂ VOL%	ART. CAP. VOL%	ART. SAT. %	NO.
1	6/17	J. H.	17	M	Rest 5.88	107.0	18.2	154.0	17.0	1.07	25.1	25.1	39.8	63.4	1
					Ex. 12.4	185.0	14.8	268.0	14.9	1.07	18.4		39.8	46.1	
2	6/21	C. B.	17	M	Rest 6.15	122.0	19.7	96.5	15.7	1.26	17.6	36.2	25.2	70.0	2
					Ex. 8.28	175.0	21.5	132.0	15.9	1.34	14.5	36.9	25.2	57.0	
3	6/25	C. G.	9	F	Rest 7.30	129.0	17.6	92.4	12.7	1.38	16.5	29.9	34.2	48.4	3
					Ex. 16.5	218.0	13.3	147.0	8.9	1.47	13.2	31.5	34.2	38.8	
4	7/1	J. O.	18	M	Rest 4.77	91.4	32.0	105.0	36.8	0.86	25.8	41.1	33.3	77.4	4
					Ex. 7.51	138.0	30.8	148.0	33.1	0.92	20.0	44.8	33.3	60.4	
5	7/8	V. H.	5	M	Rest 6.18	120.0	19.4	139.0	22.5	0.83			20.0	89.0	5
					Ex. 16.12	295.0	18.1	276.0	17.0	1.06			20.0	48.0	
6	7/10	D. F.	12	M	Rest 4.96	134.0	26.9	109.0	21.8	1.23	19.4	41.3	24.3	80.0	6
					Ex. 7.46	184.0	24.7	253.0	33.9	0.72	12.2	45.2	24.3	50.1	
7	7/16	J. F.	8	F	Rest 3.69	77.0	20.8	76.4	20.7	0.99	21.1	35.1	31.5	66.0	7
					Ex. 12.45	195.8	15.7	158.0	12.6	1.24	12.0	41.4	31.5	31.2	
8	7/22	J. F.	16	M	Rest 4.68	141.7	30.2	122.7	26.5	1.12	21.0	39.8	26.7	78.6	8
					Ex. 8.29	198.9	24.0	166.4	20.3	1.15	14.4	42.3	26.7	54.1	
9	7/24	E. R.	17	F	Rest 4.47	104.6	23.4	95.4	21.3	1.14	24.6	32.5	29.0	84.7	9
					Ex. 11.33	178.2	15.7	165.2	14.6	1.08	17.1	34.8	29.0	59.1	
10	8/5	B. H.	8	F	Rest 6.18	102.0	16.5	88.2	14.3	1.15	17.1	37.6	23.3	73.4	10
					Ex. 11.25	194.0	18.0	164.0	15.3	1.18	14.3	45.3	23.3	18.7	
11	9/6	V. B.	14	F	Rest 4.42	87.4	19.7	121.0	27.6	0.71	21.1	35.0	28.2	75.3	11
					Ex. 17.1	198.0	11.6	106.0	6.2	1.87	10.4	38.0	28.2	36.9	
12	9/16	R. W.	18	M	Rest 7.68	150.0	19.5	102.5	16.4	1.18	26.8	31.0	33.0	81.0	12
					Ex. 11.32	238.0	20.7	215.0	19.0	1.09	20.4	34.9	33.0	61.8	
13	9/21	R. F.	10	F	Rest 5.1	106.0	20.8	122.0	23.9	0.96	24.2	39.4	34.2	70.9	13
					Ex. 8.96	182.0	20.4	182.0	20.4	1.0	22.8	37.8	34.2	67.0	
14	9/24	F. C.	14	F	Rest 7.3	114.0	15.5	99.0	13.5	1.5	18.4	30.3	26.6	69.1	14
					Ex. 11.1	167.0	14.8	153.5	13.7	1.1	17.1	30.4			
15	10/2	J. M.	10	M	Rest 6.97	145.6	20.9	133.5	19.1	1.09	14.3	40.9	24.5	58.5	15
					Ex. 15.6	198.1	12.7	140.2	8.9	1.42	8.3	35.2	24.5	33.8	
16	10/22	A. S.	21	F	Rest 3.9	82.5	21.1	93.0	23.9	0.89	18.0	35.4	24.1	74.8	16
					Ex. 11.9	228.0	20.9	183.0	16.8	1.24	12.0	36.6	24.1	50.0	
17	10/30	A. O.	12	M	Rest 4.3	82.0	19.0	99.0	23.0	0.83	19.6	36.1	30.4	64.5	17
					Ex. 13.2	210.0	15.8	244.0	18.4	0.85	14.3	33.8	30.4	47.0	
18	11/9	S. C.	14	M	Rest 4.6	93.5	20.3	90.0	19.5	1.00	23.1	34.0	25.5	91.0	18
					Ex. 9.9	210.0	21.1	222.0	22.5	0.93	19.1	36.1	25.5	74.5	
19	11/13	A. H.	9	F	Rest 5.07	139.0	26.0	113.5	22.3	1.2	17.3	40.6	28.0	61.8	19
					Ex. 13.2	249.5	18.9	214.5	16.3	1.16	15.4	41.6	28.5	54.2	
20	11/15	E. L.	20	F	Rest 5.32	130.0	24.4	157.0	29.7	0.80	22.8	35.0	27.7	82.5	20
					Ex. 7.78	175.0	22.5	248.0	32.0	1.72	11.7	36.1	27.7	42.5	
21	12/3	A. C.	15	M	Rest 5.27	95.5	18.1	89.5	16.9	1.06	17.9	30.8	33.4	44.0	21
					Ex. 11.55	147.5	12.7	156.5	13.5	0.95					

this individual the ratio of oxygen consumed per liters of ventilation rose from 16.4 to 19.0. This indicated that the collateral circulation

combined with the flow through the pulmonary artery was adequate to cope with the increased respiratory demands of exercise. Table IV demonstrates that in 14 of 21 patients the respiratory quotient rose during exercise. This is in contrast to the observations of Cournand and Richards (9) who found a slight fall in normal individuals. An explanation for this observation is not possible at present.

In every instance the measurement of the breathing requirements described above was accompanied by a comparison of the oxygen and carbon dioxide contents obtained from arterial blood drawn preceding and following the standard exercise. In contrast to normal individuals (9), the patients studied in this series showed a marked decline in arterial oxygen saturation, and a rise in carbon dioxide content following the exercise (Table IV and Fig. 6). Similar results were observed in patients with large collateral circulation, in cases belonging to Eisenmenger's syndrome, and in some of the patients after the performance of the Blalock-Taussig operation (10). This demonstrated that the fall in arterial oxygen saturation after exercise observed in patients with normal rate of flow through the lung must have been caused by increased shunting of venous blood into the systemic circulation.

DISCUSSION

The results of the tests described in the preceding paragraphs demonstrate a reduction in pulmonary artery flow of from 1000 to 2000 cc. below normal cardiac index, depending on the degree of the stenosis. In one patient (#12, Table I) in whom the calculated rate of flow through the pulmonary artery is only 20 per cent of normal, atresia of that vessel was found at operation. The systemic flow, calculated per square meter of body surface, shows marked variations above and below values for normal cardiac index (Table I). In normal individuals, variations in the overall circulating volume of blood flow are usually the result of functional changes. With varying degrees of pulmonic stenosis and interventricular septal defect, however, the systemic blood flow depends to a large extent on the volume of the intracardiac shunt (Fig. 1). Table I illustrates that in most cases of tetralogy of Fallot the systemic flow exceeds that through the pulmonary artery, indicating that the overall direction of the intracardiac shunt is from right to left. Consequently the systemic blood flow will be partic-

ularly high in individuals with severe pulmonic stenosis, large interventricular septal defects, and marked overriding of the aorta. In patients with a moderate degree of pulmonic stenosis and small septal defects, where the aorta arises chiefly from the left ventricle, the systemic flow will approach normal. It will be decreased in cases of uncomplicated pulmonic stenosis where both systemic and pulmonary artery flows must be reduced below normal by an equal amount. It is apparent, therefore, that the hemodynamics of the systemic flow in tetralogy of Fallot depend to a large extent on mechanical factors brought about by the cardiac malformation.

The results obtained from an application of the indirect Fick principle to the determination of pulmonary capillary flow indicate that in some cases of tetralogy, as in normal individuals (10), the values obtained with this method agree closely with those determined for pulmonary artery flow. This demonstrates the absence of measurable collateral circulation to the lung in these individuals. In the majority of patients with pulmonic stenosis, however, pulmonary capillary flow exceeds pulmonary artery flow, indicating that the lung receives a considerable flow of blood from sources other than the pulmonary artery (Fig. 1). Collateral circulation in these individuals represents an important physiological mechanism in offsetting the effect of pulmonic stenosis by increasing the flow of mixed venous blood through the lung. The anatomical character of these collaterals is of considerable interest. Large bronchial arteries are commonly observed in these patients. In one case (#6, Table II) which shows a large calculated difference between pulmonary capillary and pulmonary artery flow, innumerable collaterals were seen to pass from intercostal and mammary arteries to the lung at operation. It is significant that in several individuals extensive collateral circulation has been responsible for the erroneous clinical diagnosis of Eisenmenger's syndrome. On fluoroscopy expansile pulsations which are characteristic in Eisenmenger's syndrome are also frequently observed in individuals with large collateral circulation.

The value of combining the determination of pulmonary artery with pulmonary capillary flow is demonstrated further in 4 patients (#4, 9, 19, 20, Table II), in whom clinical evidence suggests the presence of a patent ductus in addition to pulmonary stenosis. In

these individuals the volume of flow through the ductus is represented by the difference between pulmonary capillary and pulmonary artery flow (Fig. 2). An estimation of the rate of blood flow through the patent ductus is of considerable importance as surgical construction of an additional ductus by the Blalock-Taussig operation might be indicated if the natural anastomosis is too small.

Intraventricular pressure curves obtained in pulmonary stenosis reveal the systolic pressure in the right ventricle to be 20 to 110 mm. Hg above normal values. In most instances the pressure rises sharply and falls rapidly during the ejection phase (Fig. 3). A large series of recordings show characteristic features of right ventricular failure. This is demonstrated by the observation that in 8 out of a total of 22 recordings the general level of the ventricular diastolic pressure is elevated above the minimum values which occur early in diastole.

In cases where the catheter is passed into the pulmonary artery through the stenosis, a sharp fall in pressure is observed (Fig. 3). In 3 subjects in whom the catheter was passed from the right ventricle into the overriding aorta, complete agreement in the height of the two systolic pressures was obtained (Fig. 4). Since the oxygen contents of right ventricular blood fall within range of those in the femoral artery in some cases (Table I), it can be assumed that in these instances extensive interventricular admixture of blood leads to equilibration of pressures and gas blood concentrations of the two chambers. This conclusion is similar to that reached by Richards in his patient with tetralogy of Fallot (11).

The results summarized in Table III illustrate that the peripheral resistance varies from 600 to 6000 dynes/sec/cm⁵/M². The mean systemic pressure, on the other hand, shows only small variations from the normal. According to Aperia's mathematical expression of Poiseuille's law (4), the blood flow must vary inversely with the resistance if the pressure remains constant. Figure 5 illustrates this relationship in the patients studied. As the systemic flow increases, the peripheral resistance declines logarithmically. The importance of mechanical factors in determining the volume flow through the systemic circulation has been discussed in one of the preceding paragraphs; therefore, the variations in peripheral resistance may be considered as circulatory adjustments to changes in volume flow.

The decrease of the oxygen consumption in individuals with tetralogy of Fallot is of considerable interest since it might represent a physiological adaptation to chronic anoxia. The anoxemia observed in these patients may be compared to that present in anoxemia of high altitude. It is believed at the present moment that the oxygen consumption is independent of variations in barometric pressure (8). Only Ogata (7) reports a decrease of the oxygen consumption of rabbits exposed to severe anoxia, and Lilienthal and Riley (6) describe a slight fall in the oxygen consumption of men subjected to low oxygen tensions for short periods of time. Most observations of respiratory metabolism in anoxia in man extend of necessity for periods of several hours or days only. In individuals with cyanotic heart disease, however, the anoxia, usually present from birth, is of much longer duration. It is conceivable, therefore, that the time factor may play a rôle in the decrease of the basal metabolic rate during anoxia. Another possible explanation for the reduction of the basal metabolism in individuals with the cyanotic type of congenital heart disease may be found in the generally poor nutritional status of these patients. A great many are underweight and in some of them the restriction of physical activity is accompanied by a low caloric intake. It has been shown by a number of workers that chronic undernutrition can produce a reduction in the basal metabolic rate (12). It is impossible at present to ascertain which factors are responsible for the decrease in respiratory metabolism. Studies are under way to elucidate this problem.

Table IV shows that in 14 of 21 cases the ratio of oxygen consumed per liters of ventilation falls during the standard exercise test of Cournand and Richards (9). The ratio of carbon dioxide produced per liters of ventilation also declines during exercise in 16 patients (Table IV and Fig. 6). It is probable that the fall in these ratios is the result of the pulmonic stenosis which limits the effective pulmonary blood flow during exercise. As a result, the oxygen consumption and carbon dioxide production cannot rise in proportion to the increase in the minute volume of respiration. In patients in whom the ratio of oxygen consumed per liters of ventilation remains constant or rises, pulmonary artery flow is either normal, or large collateral circulation supplies enough mixed venous blood to take care of the increased respiratory demands of exercise.

The arterial oxygen saturation decreases in every instance immediately following the standard exercise (Table IV and Fig. 6). Simultaneously the arterial carbon dioxide content increases. Inadequate effective pulmonary blood flow which causes the decline in the ratios of oxygen consumed and carbon dioxide produced per liters of ventilation, cannot be responsible for the changes in arterial blood

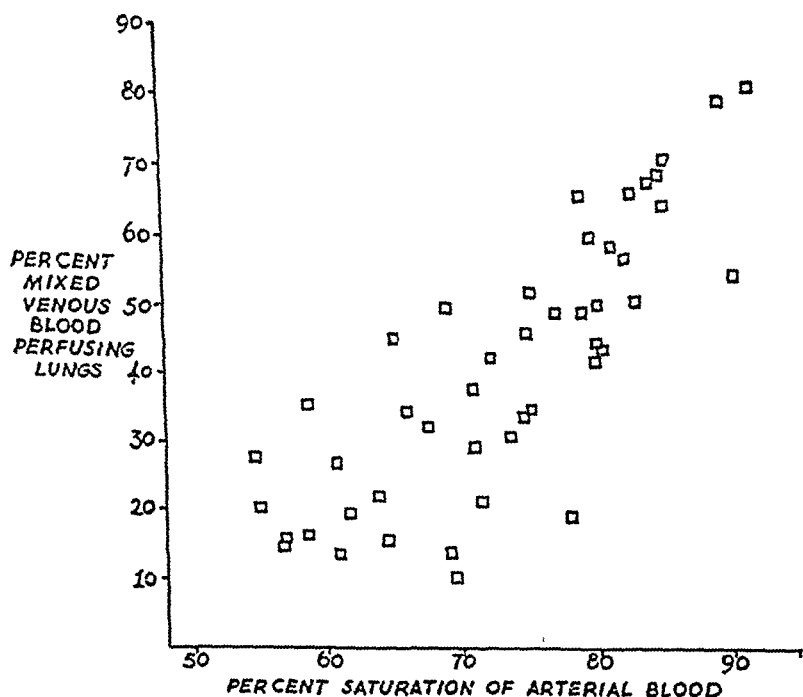


FIG. 7. represents the effect of changes in the percentage of total mixed venous blood perfusing the lung on the arterial oxygen saturation of 46 patients with tetralogy of Fallot. As the percentage of the total mixed venous flow which reaches the pulmonary epithelium increases, the arterial oxygen saturation also rises.

gases. Even in severely anoxic patients the blood reaching the left auricle is fully saturated with oxygen (1). It is therefore probable that shunts through the interventricular septal defect and the overriding aorta are responsible for the fall in oxygen saturation and the rise in carbon dioxide content of arterial blood during exercise. Additional evidence for this assumption is furnished by observations in patients

with Eisenmenger's syndrome and in some postoperative cases of tetralogy of Fallot, where the pulmonary flow is normal. Here too the standard exercise results in a fall in arterial oxygen saturation. Moreover, adequate pulmonary capillary flow is indicated by a rise in the ratio of oxygen consumed and carbon dioxide produced per liters of ventilation. In cases of interventricular septal defect, admixture of unsaturated with fully oxygenated blood is responsible for a fall in the arterial oxygen saturation. Therefore, a comparison of the gas exchange and minute volume with the arterial oxygen saturation at rest and during exercise is of great value in the recognition of the nature of the cardiac defect.

The preceding discussion has stressed the interrelationship of venous-arterial shunts and decreased pulmonary blood flow in the production of anoxemia. Further considerations indicate that the basic action of both factors is through their effect on volume of mixed venous flow through the lung (the effective pulmonary blood flow). This, as defined in the preceding communication (1), represents the volume of systemic blood which, after passing through the right auricle, reaches the alveolar capillaries. It is seen in Figure 7 that the arterial oxygen saturation is a direct function of the percentage of the total mixed venous blood which passes through the lung. On the basis of this relationship, a decrease in pulmonary capillary flow existing in conjunction with intracardiac shunts contributes to arterial oxygen saturation only by reducing the effective pulmonary blood flow. A large right to left shunt will cause anoxemia for the same reason. In uncomplicated pulmonic stenosis reduction in pulmonary flow alone, however, does not produce arterial oxygen unsaturation, since in such a case all the mixed venous blood reaches the alveolar capillaries.

SUMMARY

120 patients with tetralogy of Fallot have been studied. The results of physiological studies in 48 consecutive cases have been presented.

The blood flow through the pulmonary artery was found to be reduced in relation to the degree of stenosis. The systemic flow ranged above and below values for normal cardiac index. The variations in the systemic flow were related to the size of the intracardiac shunt, which was directed from right to left.

In most cases pulmonary capillary flow exceeded pulmonary artery flow, demonstrating the presence of collateral circulation to the lung.

The systolic pressure in the right ventricle was elevated and approximated the systolic pressure in the systemic circulation. In some instances diastolic pressures were also above normal. As the systemic mean blood pressure was within normal range, the peripheral resistance varied logarithmically with the systemic flow.

The basal metabolic rate was below normal. The possible reasons for this finding were discussed.

During the standard exercise test the ratios of oxygen consumed and of carbon dioxide produced per liters of ventilation decreased, while the arterial oxygen saturation dropped immediately following the exercise. The diagnostic significance of this test was discussed.

The importance of the effective pulmonary blood flow in the production of anoxemia was emphasized.

BIBLIOGRAPHY

1. BING, R. J., VANDAM, L. D., AND GRAY, F. D., JR.: Physiological Studies in Congenital Heart Disease. I. Procedures. This journal.
2. CURNAND, A.: Measurement of Cardiac Output in Man Using Right Heart Catheterization; Description of Technique; Discussion of Validity and of Place in Study of Circulation. *Federation Proc.*, 4: 207, 1945.
3. BLALOCK, A.: Personal communication.
4. APERIA, A.: Hemodynamic Studies. *Skandinav. Arch. f. Physiol.*, Supplement 16 (to vol. 83), 1940.
5. DEXTER, L.: Personal communication.
6. LILIENTHAL, J. L., JR., RILEY, R. L., PROEMMEL, D. D., AND FRANKE, R. E.: An Experimental Analysis in Man of the Oxygen Pressure Gradient from Alveolar Air to Arterial Blood During Rest and Exercise at Sea Level and at Altitude: *Am. J. Physiol.* 147: 199, 1946.
7. OGATA, H.: Anoxemia. I. Influence of Acute Anoxic Anoxemia with Oxygen-Poor Air on Respiration. *J. Biophysics (Japan)*, 1: 1, 1923.
8. VAN LIERE, E. J.: Anoxia. Its Effect on the Body. University of Chicago Press, 1942. P. 196.
9. CURNAND, A., AND RICHARDS, D. W., JR.: Pulmonary Insufficiency. Discussion of the Physiological Classification and Presentation of Clinical Tests. *Am. Rev. Tuberc.* 44: 26, 1941.
10. BING, R. J., VANDAM, L. D., AND GRAY, F. D., JR.: Unpublished observations.
11. RICHARDS, D. W., JR.: Congenital Heart Disease; Measurements of the Circulation. *Arch. Int. Med.* 47: 484, 1931.
12. DU BOIS, E.: Basal Metabolism in Health and Disease. Philadelphia: Lea and Febiger, 1936.

THE LIPOTROPIC EFFECT OF N¹-METHYLNICOTINAMIDE¹

VICTOR A. NAJJAR AND IDALINE M. RATCLIFFE

From the Department of Pediatrics, Johns Hopkins Medical School and The Harriet Lane Home, Johns Hopkins Hospital, Baltimore, Maryland

It has been shown that the F₂ product of nicotinamide metabolism (1, 2, 3) is a methylated compound, namely N¹-methylnicotinamide (4, 5, 6). Since this compound is a normal constituent of body tissue and body fluids, it became desirable to ascertain whether this methylation reaction that takes place in the liver (7, 8) is a reversible one.

In an earlier report Najjar and Deal (9) showed that when 2% N¹-methylnicotinamide chloride was fed to a small group of rats, incorporated in a diet containing glycocyamine, the amount of fat deposited in the livers of those rats was appreciably lower than that obtained in the control animals not receiving the methyl compound. Handler and Dubin (10), using a different diet supplemented with 1% N¹-methylnicotinamide alone or with homocystine, did not obtain any lipotropic activity. To test this effect further additional experiments were performed using a larger group of rats.

EXPERIMENTAL

Three types of experiments were performed. They were designed to show 1) the effect of N¹-methylnicotinamide alone on liver lipids, 2) the effect of N¹-methylnicotinamide in conjunction with glycocyamine as a methyl acceptor and 3) to investigate the possibility that the drug might act as a vitamin analogue, producing nicotinamide deficiency. In this case a deficiency would produce, among other signs, a failure of appetite and a retardation of growth and thereby indirectly affect fat deposition in the liver.

In all experiments, newly weaned 3-4 week old male rats were used. Litter mates were divided between the controls and the test animals. All rats were placed in wire cages with screened bottoms. They were allowed free access to water and diet. Their weights and food intake were recorded daily. The first strain of rats employed suffered a high mortality on the diet and could not be used for this experiment.

¹ Aided by a grant from Mead Johnson and Company, Evansville, Indiana.

Another strain² was more satisfactory and was used successfully throughout this study. The basal diet was that of Griffith and Wade (11) and consisted of vitamin free casein 15 parts by weight, crisco 35, sucrose 32, Cox and Imboden's salt mixture (12) 4, calcium carbonate 1, agar 2, cod liver oil 5 and yeast 6. This diet was supplemented with N¹-methylnicotinamide chloride alone or in conjunction with either glycocyamine or nicotinamide. The dosage of glycocyamine varied from 5-10 mM per kilogram of diet, that of N¹-methylnicotinamide from 2-4% (Table I and II) and nicotinamide from 0.4-0.8%. For the sake of simplicity, rats fed a supplemented diet will be referred to as supplemented rats. After a number of weeks on the experiment the animals were killed by chloroform, wet weights of their livers obtained and slices weighing no less than 2.5 grams were taken for fat estimation. Each specimen was individually assayed by continuous chloroform extraction (13) for eight hours. The chloroform fat extracts were evaporated to dryness over a steam bath, then placed in an oven at 110°C. for twenty-four hours and lipid weights obtained.

*The effect of N¹-methylnicotinamide on liver lipids of rats
fed diet alone*

Table I shows the results obtained in three groups of rats, each comprising control animals and animals supplemented with 4% N¹-methylnicotinamide chloride. Group I received the diet for seven days and Group II and III for fourteen and twenty-eight days respectively. There were no deaths during the experiment. The animals were active and behaved normally in every way except that Group I and II showed no gain in weight in the supplemented rats.

There was no difference in the liver lipids between the controls and the supplemented rats of Group I. However, rats in Group II and III, that received the supplemented diet, showed about 4% less fat than the controls.

*The effect of N¹-methylnicotinamide on liver lipids of rat
fed diet plus glycocyamine*

Table II includes the data on five groups of rats in which the control animals ingested the diet supplemented with glycocyamine, whereas

² Procured from Research Supply Company, 2436 West York St., Philadelphia, Pa.

the test animals received 2-4% N¹-methylnicotinamide chloride in addition. Glycocyamine, 10 mM per kilogram of diet, was used in all diets except that of Group IV which contained half that amount. The experimental period varied from seven to fourteen days. The animals were active and no deaths occurred.

In contrast to the results in Table I, where no glycocyamine was included in the diet, the liver lipids in these groups were consistently lower in the animals supplemented with the N¹-methylnicotinamide than in the controls. Moreover, the gain in weight in the supplemented animals (except Group VII) were comparable to the controls.

TABLE I
The effect of N¹-methylnicotinamide on liver lipids of rats receiving diet alone

GROUP	DIET SUPPLEMENT N ¹ -METHYLNICOTINAMIDE CHLORIDE	DURATION OF EXPERIMENT	NO. OF RATS	AGE	AVER. DAILY FOOD INTAKE	AVER. GAIN IN WEIGHT	LIVER FAT % LIVER WEIGHT*	LIVER FAT % BODY WEIGHT	LIVER WEIGHT* % BODY WEIGHT
	gm. %	days		days	gm.	gm.			
I	0.0	7	5	21	5.7	11.4	12.6	0.66	5.1
	4.0	7	5	21	5.2	1.0	13.2	0.59	4.4
II	0.0	14	5	21	4.2	9.6	18.2	1.18	6.5
	4.0	14	5	21	3.4	1.4	14.4	0.72	5.0
III	0.0	28	7	21	5.0	30.5	23.1	1.94	8.0
	4.0	28	6	21	4.6	18.0	17.9	1.23	5.8

* Liver weights indicated are wet weights.

The effect of nicotinamide on rats fed diet plus N¹-methylnicotinamide

Three groups of rats were used. Group A consisted of seven rats that ingested the diet alone. Six rats, Group C, were fed diet supplemented with 4% N¹-methylnicotinamide chloride. Seven rats, Group B, received as supplement 4% N¹-methylnicotinamide chloride and 0.4% nicotinamide. On the fourteenth day the nicotinamide was increased to 0.8%. The nicotinamide was used to counteract the possible effect of N¹-methylnicotinamide as an analogue inhibitor.

It is apparent from Figure I that rats of Group A, after an initial loss, gained weight satisfactorily throughout the experiment. How-

TABLE II
The effect of N¹-methylnicotinamide on liver lipids of rats receiving Griffith and Wade diet with glycocyamine

GROUP	DIET SUPPLEMENT		DURATION OF EXPERIMENT	NO. OF RATS	AGE	AVERAGE DAILY FOOD INTAKE	AVERAGE GAIN IN WEIGHT	LIVER FAT % LIVER WEIGHT*	LIVER FAT % BODY WEIGHT	LIVER WEIGHT* % BODY WEIGHT
	N ¹ -methyl-nicotinamide chloride	Glycocyamine								
	gm. %	mlf. per kilo	days		days	gm.	gm.			
IV	0.0 2.0	5.0 5.0	14 14	9 9	21 21	4.9 4.8	31.0 29.5	12.9 9.8	0.64 0.53	5.00 5.10
V	0.0 2.0	10.0 10.0	7 7	14 14	28 28	4.6 4.3	17.0 10.0	20.4 17.5	1.27 0.86	6.13 4.95
VI	0.0 2.0	10.0 10.0	14 14	9 11	21 21	4.6 4.1	14.0 10.3	21.0 16.9	1.77 1.18	8.19 7.05
VII	0.0 4.0	10.0 10.0	7 7	7 7	21 21	4.7 3.3	13.8 3.0	22.6 14.8	1.43 0.78	6.38 5.18
VIII	0.0 4.0	10.0 10.0	14 14	7 6	21 21	4.3 4.0	15.1 10.6	29.9 15.3	2.55 0.89	8.50 5.87

* Liver weights indicated are wet weights.

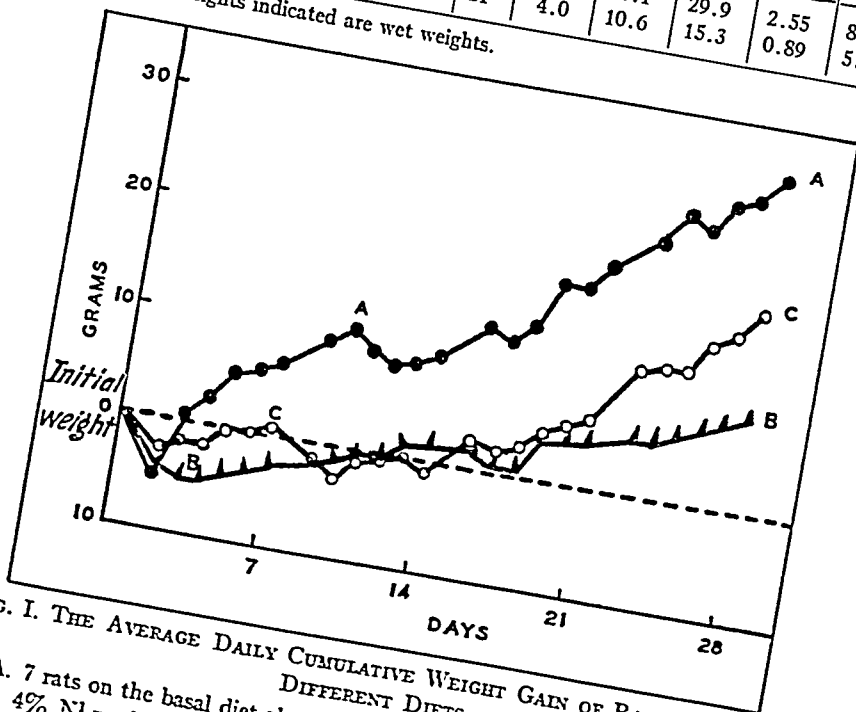


FIG. I. THE AVERAGE DAILY CUMULATIVE WEIGHT GAIN OF RATS RECEIVING DIFFERENT DIETS
A. 7 rats on the basal diet alone. B. 7 rats on the basal diet supplemented with 4% N¹-methylnicotinamide chloride and 0.4% nicotinamide. The latter was increased to 0.8% on the 14th day. C. 6 rats on the basal diet supplemented with 4% N¹-methylnicotinamide chloride.

ever, in Groups B and C, after a similar initial weight loss, there occurred a gain in weight with no significant difference between the two groups though less than Group A. All animals were equally active. It is clear, therefore, that N¹-methylnicotinamide did not possess a vitamin analogue effect which, at least, could be counteracted by nicotinamide.

DISCUSSION

It is clear from the results obtained that the effect of N¹-methylnicotinamide on liver fat, whatever its nature may be, is exerted only to a limited degree under the conditions of our experiment. It appears that the addition of glycocyamine to the diet favored such an effect. This is suggested particularly by the results in Group IV and VIII (Table II). In the former the dietary intake and the gain in weight were almost identical in the supplemented and control animals, although the liver lipids showed a significant difference in favor of the rats receiving the drug. Similarly, in Group VIII the liver fat value of the supplemented rats (15.3%) was much less than the controls (29.9%), although their dietary intake was comparable. It is also apparent that with the increase in the dosage of N¹-methylnicotinamide the effect on liver fat becomes more marked (Table II, Groups VII and VIII).

In attempting to explain our results several possibilities present themselves:

1. That the drug possesses an active labile methyl group. In view of the high dosage used, it is certainly not comparable to that of choline and methionine (14).

2. That the drug has a lipotropic effect without a labile methyl group.

3. Another possibility is that the N¹-methylnicotinamide, by competitive action with nicotinamide, precipitated a vitamin deficiency and thereby influenced the fatty deposition in the liver (15, 16, 17). This did not seem likely because the rats were uniformly active. Their food intake did not suggest a loss of appetite and, on the whole, was comparable to the control animals except in two instances—Group II and VII. Furthermore, as shown in Figure I, nicotinamide did not improve the gain in weight nor did the animals receiving N¹-methylnicotinamide reveal any signs of vitamin deficiency.

4. It is also possible that failure of growth may diminish liver fat deposition as suggested by Handler and Bernheim (18). This would be applicable to the N¹-methylnicotinamide treated rats since, in general, they did not gain as well as their respective controls. However, there was a significant difference in the liver fat values in Group IV (Table II) even though the gains in weight of the supplemented and control rats were identical. Conversely, the supplemented rats in Group I (Table I) showed even a higher percentage of fat despite a lack of gain in weight, whereas their controls grew normally.

5. Finally, it is possible that the effect of N¹-methylnicotinamide is a sparing effect similar to that advanced for creatine (19, 20). The diet furnished in our experiment contained methionine and choline so that a sparing effect may be evident. It would also be expected that a sparing action would become more evident when the demand on the methyl group is increased. Such was the case with the glyco-cyamine supplemented groups where the liver fat of the N¹-methylnicotinamide supplemented rats showed a more significant difference than their controls, as compared to the rats not supplemented with glyco-cyamine, particularly when 4% of the methyl compound was used.

CONCLUSION

N¹-methylnicotinamide possesses a lipotropic effect, though small in magnitude. The manner in which this action is exerted is, at present, obscure. The different possibilities are discussed.

N¹-methylnicotinamide does not possess an antinicotinamide action and therefore does not enter into competitive inhibition system with the vitamin.

BIBLIOGRAPHY

- (1) NAJJAR, V. A., AND WOOD, R. W., *Proc. Soc. Exper. Biol. and Med.*, **44**: 386, 1940.
- (2) NAJJAR, V. A., AND HOLT, L. E., Jr., *Science*, **93**: 20, 1941.
- (3) NAJJAR, V. A., AND HOLT, L. E., Jr., *Proc. Soc. Exper. Biol. and Med.*, **48**: 413, 1941.
- (4) HUFF, J. W., AND PERLZWEIG, W. A., *J. Biol. Chem.*, **150**: 395, 1943
- (5) ELLINGER, P., AND COULSON, R. A., *Nature*, **152**: 383, 1943.
- (6) NAJJAR, V. A., WHITE, V., AND SCOTT, D. B. M., *Bull. Johns Hopkins Hosp.*, **74**: 378, 1944.

- (7) PERLZWEIG, W. A., BERNHEIM, M. L. C., AND BERNHEIM, F., J. Biol. Chem. 150: 401, 1943.
- (8) NAJJAR, V. A., HALL, R. S., AND DEAL, C. C., Bull. Johns Hopkins Hosp., 76: 83, 1945.
- (9) NAJJAR, V. A., AND DEAL, C. C., J. Biol. Chem., 162: 741, 1946
- (10) HANDLER, P., AND DUBIN, I. N., J. Nutrition, 31: 141, 1946.
- (11) GRIFFITH, W. H., AND WADE, N. J., J. Biol. Chem., 132: 627, 1940.
- (12) COX, W. M., JR., AND IMBODEN, M., Proc. Soc. Exper. Biol. and Med., 34: 443, 1936.
- (13) CHANNON, H. J., PLATT, A. P., AND SMITH, J. A. B., Biochem. J., 31: 1736, 1937.
- (14) DU VIGNEAUD, V., The Harvey Lecture Series, 38: 39, 1942.
- (15) MCHENRY, E. W., J. Physiol., 89: 287, 1937.
- (16) MCHENRY, E. W., AND GAVIN, G., Science, 91: 171, 1940.
- (17) ENGLE, R. W., J. Nutrition, 24: 175, 1942.
- (18) HANDLER, P., AND BERNHEIM, F., J. Biol. Chem., 148: 649, 1943.
- (19) DU VIGNEAUD, V., CHANDLER, J. P., AND MOYER, A. W., J. Biol. Chem., 139: 917, 1941.
- (20) GRIFFITH, W. H., AND MULFORD, D. J., Proc. Soc. Exper. Biol. and Med., 45: 657, 1940.

STUDIES ON THE PROTEIN METABOLISM OF THE INFANT¹

I. THE COMPARATIVE BIOLOGICAL VALUE OF SOME MILK PROTEIN PREPARATIONS

ANTHONY A. ALBANESE, L. EMMETT HOLT, JR., VIRGINIA IRBY, SELMA E. SNYDERMAN, AND MARILYN LEIN

From the Department of Pediatrics, New York University College of Medicine and the Children's Medical Service, Bellevue Hospital, New York

The current practice of administering protein digests for total or supplemental alimentation to infants suffering from diseases which induce excessive nitrogen loss led us to undertake the testing of the nutritional quality of some available milk preparations in the normal infant. The biological value of an enzymatic digest of casein (Amigen) and lactalbumin (Edamin) as well as a tryptophane and cystine supplemented acid digest of casein were tested and compared with that of an evaporated milk formula. Bioassays of these preparations in immature rats had previously shown that both enzymatic products were nutritionally superior to the reinforced acid hydrolysate of casein.

EXPERIMENTAL

Assay Procedure. The composition and caloric distribution of the diets employed in this study are shown in Chart I. All diets were given in 5 feedings daily at the rate of about 100 calories per kilogram of body weight and were supplemented daily with 50 mg. of ascorbic acid and 15 drops of oleum percomorphum. The tryptophane and cystine supplemented acid hydrolysates of casein were prepared as previously described by some of us (1). Owing to uncertainties regarding the B complex vitamins, Brewers' yeast was used instead of a mixture of the synthetically available components of these vitamins. The quantities of amino acid derived from this source can be readily ascertained from the literature (2). Each batch of diet mixture was analyzed directly for nitrogen content by the micro-Kjeldahl method, the daily N intake of the subjects calculated from the consumption record and each diet was assayed for seven day periods. The different diet

¹ The work described in this report was supported by grants from the Rockefeller Foundation and the National Live Stock and Meat Board.

periods were consecutive and began on successive Saturday mornings. The infants, 3 normal white full-term males, were weighed daily during the course of the experiment. The urine and feces were not collected for the first two days of each period in order to avoid complications resulting from continued use of restraints and adjustment to dietary changes.

Analytical Methods. Data on the nitrogen output were obtained from micro-Kjeldahl analyses of daily 24-hour urine collections and wet-ashed 5 day pools of the feces.

CHART I. COMPOSITION OF DIET

Evaporated Milk Formula:

Evaporated milk, 40 cc. (55.3 cal.); Corn sirup 6 cc. (17.7 cal.); Water 54 cc. Total volume 100 cc. Total calories 73.

Protein Digest Formulae:

Protein digest (0.56 gm. N \times 6.25).....	3.5 gm.	14.0 calories
Mead Johnson Lab. Prod. #217.....	18.0 gm.	
Fats.....	4.0 gm.	36.0
Carbohydrates.....	11.6 gm.	46.5
Mead Johnson Brewer's Yeast.....	1.0 gm.	3.5
Water.....	88.0 cc.	
Total.....	100 cc.	100 calories

Salt supplement mg. per 100 cc.; Fe·SO₄ 10, Na·Cl 100; Ca·gluconate 790, KH₂·PO₄ 323, Ca·(OH)₂ 197, K₂·H PO₄ 108, KCl 90, Mg·O 18.

Protein Preparations Used:

Amigen, an enzymatic casein digest (Mead Johnson & Co.); Edamin, an enzymatic lactalbumin digest (Sheffield Farms Co.); CTH, acid hydrolysate of casein supplemented with 1.5 per cent of *l*-tryptophane and 1.0 per cent of *l*-cystine.

Blood samples (10 cc.) were obtained on the last day of each diet period by venapuncture. The hemoglobin content of these specimens was determined colorimetrically in the Klett-Summerson photoelectric colorimeter. The total plasma proteins, albumin and non-protein N were determined by the usual procedures (3). The globulin was estimated as the difference of total protein and albumin. The amino N content of the plasma was determined by the copper method (4).

The urinary amino acids, free amino N (5) and bound amino N (6), arginine (7), histidine (8), methionine (9), tryptophane (10), tyrosine (11), total β -hydroxyamino N (12), phenylalanine (13), and cystine

(14) were determined by chemical procedure previously reported by ourselves and others on urine pools collected during the last 4 days of each diet period. The output of urea (15), ammonia (16), organic acids (17), indican (18), free phenols (19), creatine and creatinine (20) was also measured.

RESULTS

The nitrogen balance and body weight measurements obtained in these experiments (Table I) clearly indicate that by these two criteria the nutritional quality of the CTH diet is inferior to that of the evaporated milk, edamin or amigen formulae. Interestingly enough on this basis, the biological value of the enzymatic digests of casein and lactalbumin appear to be equal to that of the evaporated milk formula for these short periods. Although it would also appear from our findings that lactalbumin is not nutritionally superior to casein, it must be noted: (a) that the removal of some amino acids in the preparation of both digests may equalize their amino acid contour; and (b) that approximately 12 per cent of the nitrogen of the synthetic diets is derived from the added Brewers' yeast which by virtue of its amino acid content may so supplement the protein components as to compensate for any limiting nutritional factors.

Our nitrogen retention values fall well within the range of those previously reported by other workers using a variety of milk formulae (Table II). However, our results are somewhat higher than those of Shohl, Butler, Blackfan and MacLachlan (24) who found that the N retention of infants 2 to 7 months of age was only slightly altered by substitution of a synthetic formula composed of amigen, carbohydrates and fats for an evaporated milk formula when both were fed at the same fluid, caloric and nitrogen levels. The average intakes from these diets amounted to 520 mg. of N per kilogram and resulted in average nitrogen retentions of 140 mg. and 170 mg. of N per kilogram of body weight for the amigen and evaporated milk formulae respectively. The differences between our results and those of Shohl and associates may arise from our use of Brewers' yeast rather than the synthetic vitamin B complex mixture employed by Shohl or from the higher nitrogen intake of our subjects. The latter possibility is supported by the well known fact that the N retention of infants can be readily elevated by

increasing the N intake. This phenomenon is not only apparent for short periods of time but has also been shown by Nelson (22) to lead to the development of larger but not necessarily better babies.

In studies of protein metabolism, nutritional adequacy of the nitrogen component of the diet in the growing or mature organism is commonly measured in terms of weight change and nitrogen balance. In spite of the evidence presented by Folin (25) and others (26), it has

TABLE I
Effect of Various Protein Digests on the Nitrogen Economy of the Infant
(Results given as daily averages)

INITIAL AGE AND WEIGHT OF SUBJECT	DIET	AVER- AGE PERIOD WEIGHT	DAILY WEIGHT GAIN	INTAKE PER KG.		TOTAL NITROGEN INPUT	NITROGEN OUT- PUT			NITROGEN RETEN- TION	TISSUE DEPOS- ITION
				Volume	Nitrogen		Urine	Feces	Total		
A. J. 11 mos. 9,618 gm.	Evaporated milk	9,707	25.6	112	0.63	6.12	3.68	0.58	4.26	193	41.5
	Amigen	9,896	28.3	95	0.62	6.08	3.15	0.97	4.12	197	44.0
	Edamin	10,094	28.3	95	0.61	6.09	3.50	0.80	4.30	178	40.8
	CTH	10,262	19.9	103	0.65	6.65	4.43	0.88	5.31	130	44.8
P. D. 6 mos. 6,484 gm.	Evaporated milk	6,584	28.4	152	0.68	4.47	2.52	0.53	3.05	217	60.0
	Amigen	6,789	30.1	103	0.63	4.30	2.50	0.52	3.02	189	71.4
	Edamin	6,694	28.4	104	0.64	4.25	2.60	0.46	3.06	180	71.4
	CTH	7,136	12.0	100	0.69	4.96	3.46	0.47	3.93	140	36.0
D. R. 5 mos. 6,620 gm.	Evaporated milk	6,721	29.0	140	0.63	4.22	2.32	0.55	2.87	200	65.1
	Amigen	6,923	28.9	100	0.60	4.15	2.53	0.31	2.84	189	66.8
	Edamin	7,120	27.2	100	0.60	4.29	2.28	0.63	2.81	208	55.8
	CTH	7,281	16.0	102	0.69	5.01	3.33	0.63	3.96	144	48.0

been assumed by some investigators that these two biological functions should vary in direct proportion. Such a view fails to acknowledge the obvious possibility that tissue water and fat depots can be mobilized independently of body proteins. This possibility of divergences of weight change and nitrogen retention is supported experimentally by the often repeated observations that weight gain in infants and children is usually 60 per cent of that calculated from the nitrogen retention

according to Rubner's Law, that one gram of nitrogen is equivalent to 33 gm. of body substance (27). Thus it will be noted that tissue deposition estimated as $\text{grams daily weight change} \times 100/\text{grams daily N retention} \times 33$, approximate 59 per cent as a mean value for the evaporated milk, amigen and edamin diets, but falls below this figure for the CTH diets. The biological function of the retained nitrogen not accounted for by weight accretion should be investigated.

Examination of the data in Table III reveals that the inferior quality of the CTH diet is not reflected by any significant changes in blood

TABLE II

Comparison of Observed Nitrogen Retention of Infants on Various Cow's Milk Preparations

INVESTIGATORS	DIET	AGE GROUP	NITROGEN	
			Intake	Retention
		<i>weeks</i>	<i>mg./kg.</i>	<i>mg./kg.</i>
Authors	Karo modified evaporated milk	20-45	630-680	193-217
	Synthetic amigen formula	20-45	600-630	189-197
	Synthetic edamin formula	20-45	600-640	178-208
	CTH formula	20-45	650-690	130-140
Daniels and Hejninian (21)	Dextri-maltose modified, cow's milk	5-35	485-565	86-168
Nelson (22)	Acidified undiluted cow's milk	5-45	530-688	123-211
Jeans and Stearns (23)	Acidified diluted evaporated milk	5-45	495-640	113-201

protein levels. This finding is in accord with our previous observation that in the rat (1) the suboptimal biological value of diets prepared with tryptophane and cystine supplemented acid digests of casein failed to affect adversely their blood protein levels. Attention is also called to the finding that amino N levels of blood were not elevated as a result of the feeding of either the acid or enzymatic protein digests above the levels found during the evaporated milk feedings nor did the ratio of amino N to total non-protein nitrogen show any significant fluctuations with dietary changes.

In order to determine possible differences in the metabolism of the various milk protein preparations tested, measurements of urinary

amino acids and other metabolites were made. Thus it was observed that the output of ammonia, urea, arginine, cystine, phenylalanine, tyrosine, total hydroxyamino N, indican, free phenols, creatinine and creatine was not significantly altered by changes in the protein moiety of the diet. On the other hand, the excretion of the urinary constituents listed in Table IV was affected by shifts in the diet. Examination of these data reveals that feeding of CTH diet induced a rise in the free

TABLE III

Effect of Various Protein Digests on Blood Proteins of the Infant

SUBJECT	DIET	TOTAL PLASMA PROTEIN	ALBUMIN	GLOBULIN	A/G RATIO	NON-PROTEIN NITROGEN	HEMOGLOBIN	AMINO NITROGEN
		<i>gm. per cent</i>	<i>gm. per cent</i>	<i>gm. per cent</i>		<i>mg. per cent</i>	<i>gm. per cent</i>	<i>mg. per cent</i>
A. J.	Evaporated milk	6.03	3.45	2.58	1.34	31.5	8.7	8.85
11 mos.	Amigen	6.37	3.97	2.40	1.66	24.7	8.8	8.53
9,618 gm.	Edamin	6.47	3.57	1.90	1.92	27.7	8.5	7.42
	CTH	5.88	3.41	2.47	1.38	29.1	8.5	7.00
P. D.	Evaporated milk	5.29	3.52	1.77	1.99	27.3	9.6	7.56
6 mos.	Amigen	5.06	2.97	2.09	1.42	22.2	7.7	8.30
6,484 gm.	Edamin	5.25	3.17	2.08	1.52	25.0	8.8	8.71
	CTH	5.64	4.05	1.59	2.54	28.9	8.4	8.05
D. R.	Evaporated milk	6.13	3.85	2.28	1.68	27.5	10.4	8.62
5 mos.	Amigen	5.70	3.13	2.57	1.22	20.8	8.6	7.30
6,620 gm.	Edamin	5.81	3.25	2.56	1.27	19.9	9.7	8.69
	CTH	5.88	3.78	2.10	1.80	30.3	9.7	7.70

and bound amino N, methionine, histidine, tryptophane and organic acid levels of the urine above those found with the other three diets. It seems reasonable to associate this phenomenon with the inferior nutritional properties exhibited by the CTH diet and therefrom to interpret the increase in bound amino N to represent protein fragments, possibly polypeptides, which owing to the lack of some nutritional component in this diet failed to be synthesized into normal protein

molecules. Moreover, it would appear that the biosynthetic failure also causes the urinary loss of methionine, histidine and tryptophane, amino acids which normally would presumably be utilized in the formation of complete proteins. The increase in urinary organic acid titre also observed with the CTH diet seems to be derived for the most part from the amino acid increase.

TABLE IV
Effect of Various Protein Digests on the Urinary Metabolites of the Infant

SUBJECT	URINARY METABOLITES	EVAPOR- ATED MILK	AMIGEN	EDAMIN	CTH
A. J.	Total N, gm.	3.68	3.15	3.50	4.43
11 mos.	Free amino N, mg.	116	69	104	132
	Methionine, mg.	81	63	78	123
	Histidine, mg.	89	95	90	117
9,618 gm.	Tryptophane, mg.	31	21	24	58
	Bound amino N, mg.	150	132	142	323
	Organic acids, cc. 0.1 N HCl	124	101	104	268
P. D.	Total N, gm.	2.52	2.50	2.60	3.46
6 mos.	Free amino N, mg.	67	151	113	175
	Methionine, mg.	42	54	32	109
	Histidine, mg.	63	96	40	118
6,484 gm.	Tryptophane, mg.	14	17	30	34
	Bound amino N, mg.	160	152	163	360
	Organic acids, cc. 0.1 N HCl	141	177	167	220
D. R.	Total N, mg.	2.32	2.53	2.28	3.33
5 mos.	Free amino N, mg.	73	111	102	136
	Methionine, mg.	70	45	49	105
	Histidine, mg.	68	87	32	110
6,620 gm.	Tryptophane, mg.	13	16	18	27
	Bound amino N, mg.	170	152	136	308
	Organic acids, cc. of 0.1 N HCl	99	129	126	156

COMMENTS

Previous reports (28) from this laboratory indicated that diets prepared with mixtures of the crystalline amino acids or tryptophane and cystine supplemented acid hydrolysates of the proteins induced about 50 per cent of the growth in the immature rats as that of diets constructed from enzymatic digests of the proteins or whole proteins.

The findings reported here indicate that the CTH diet also exhibits a suboptimal biological value in the infant. Recent work by Woolley (29) has shown that the optimal growth characteristics of diets prepared from whole or enzymatically digest proteins are due to peptide-like substances, strepogenin, occurring in these products. Consideration of our present observations on the CTH diet in the light of Dr. Woolley's work prompts the speculation that the strepogenin fraction is also required by the infant for maximal utilization of the dietary amino acids. These thoughts must, however, be tempered by a cognizance of the fact that the suboptimal biological value of our CTH diet may arise in part, if not entirely, from the loss of amino acids themselves during the preparation of the acid hydrolysate of casein.

SUMMARY

It has been observed that the nitrogen retention and weight gain of 3 normal infants maintained on a synthetic diet in which a tryptophane and cystine reinforced acid digest of casein constituted the principal source of nitrogen were respectively about 30 and 50 per cent lower than those obtained when the same subjects were fed synthetic diets at the same fluid, caloric distribution and nitrogen levels in which enzymatic digests of casein or lactalbumin supplied the principal nitrogen component. The biological value of these latter two diets as indicated by the criteria of weight accretion and nitrogen storage appears for short periods to be equal to that of diluted evaporated milk formula and to that found by previous investigators employing various modifications of cow's milk. The inferior nutritional quality of the acid casein digest diet was not reflected in the blood protein levels of our subjects. The possible relationship of the poor biological value of this diet to the observed higher output of urinary bound amino N and free amino acids is discussed.

We wish to thank Mrs. Barbara Saur and Miss Adele Alpy for their assistance in this work.

BIBLIOGRAPHY

1. ALBANESE, A. A., HOLT, L. E., JR., KAJDI, C. N., AND FRANKSTON, J. E.: *J. Biol. Chem.*, **148**, 299 (1943).
2. CARTER, H. E., AND PHILLIPS, G. E.: *Fed. Proc.*, **3**, 123 (1944).

3. ROBINSON, H. W., PRICE, J. W., AND HAGDEN, C. G.: J. Biol. Chem., 120, 481 (1937).
4. ALBANESE, A. A., AND IRBY, V.: J. Lab. Clin. Med., 30, 718 (1945).
5. ALBANESE, A. A., AND IRBY, V.: J. Biol. Chem., 153, 583 (1944).
6. ALBANESE, A. A., HOLT, L. E., JR., FRANKSTON, J. E., AND IRBY, V.: Fed. Proc., 5, 118 (1946).
7. ALBANESE, A. A., AND FRANKSTON, J. E.: J. Biol. Chem., 159, 185 (1945).
8. ALBANESE, A. A., FRANKSTON, J. E., AND IRBY, V.: J. Biol. Chem., 160, 441 (1945).
9. ALBANESE, A. A., FRANKSTON, J. E., AND IRBY, V.: J. Biol. Chem., 156, 293 (1944).
10. ALBANESE, A. A., AND FRANKSTON, J. E.: J. Biol. Chem., 157, 59 (1945).
11. ALBANESE, A. A., IRBY, V., AND LEIN, M.: J. Biol. Chem., *in press*.
12. ALBANESE, A. A., IRBY, V., AND LEIN, M.: *Unpublished data*.
13. ALBANESE, A. A.: J. Biol. Chem., 155, 291 (1944).
ALBANESE, A. A.: Bull. Johns Hopkins Hosp., 75, 175 (1944).
14. SULLIVAN, M. X., AND HESS, W. C.: J. Biol. Chem., 116, 221 (1936).
15. BARKER, S. B.: J. Biol. Chem., 152, 453 (1944).
16. ALBANESE, A. A.: J. Lab. and Clin. Med., 29, 447 (1944).
17. VAN SLYKE, D. D., AND PALMER, W. W.: J. Biol. Chem., 41, 567 (1920).
18. SHARLIT, H.: J. Biol. Chem., 99, 537 (1932).
19. MARENZI, A. D.: C. R. Soc. Biol., 107, 734 (1931).
20. ALBANESE, A. A., AND WANGERIN, D. M.: Science, 100, 58 (1944).
21. DANIELS, A. L., AND HEJNIAN, L. M.: Am. J. Dis. Child., 38, 499 (1929).
22. NELSON, M. U. K.: Am. J. Dis. Child., 39, 70 (1930).
23. JEANS, P. S., AND STEARNS, G.: Am. J. Dis. Child., 46, 69 (1933).
24. SHOHL, A. T., BUTLER, A. M., BLACKFAN, K. D., AND MACLACHLAN, E.: J. Ped., 15, 469 (1939).
25. FOLIN, O.: Am. J. Physiol., 13, 100 (1905).
26. MACY, I. G.: Nutrition and Chemical Growth in Childhood. I, Evaluation, Springfield, pp. 153-5 (1942).
JOHNSON, J. A.: Am. J. Dis. Child., 59, 287 (1940).
27. RUBNER, M.: Arch. J. Hyg., 66, 45 (1908).
28. ALBANESE, A. A., AND IRBY, V.: Science, 98, 286 (1913).
ALBANESE, A. A., AND FRANKSTON, J. E.: Bull. Johns Hopkins Hosp., 77, 61 (1945).
ALBANESE, A. A., HOLT, L. E., JR., IRBY, V., AND BRUMBACK, J. E., JR.: J. Biol. Chem., 165, 179 (1946).
29. WOOLLEY, D. W.: J. Biol. Chem., 159, 753 (1945); J. Biol. Chem., 162, 383 (1946).

STUDIES ON THE PROTEIN METABOLISM OF INFANTS¹

II. TRYPTOPHANE REQUIREMENT OF THE INFANT

ANTHONY A. ALBANESE, L. EMMETT HOLT, JR., VIRGINIA IRBY,
SELMA E. SNYDERMAN AND MARILYN LEIN

*From the Department of Pediatrics, New York University College of Medicine and the
Children's Medical Service, Bellevue Hospital, New York*

Although it has long been known that on a body weight basis the protein requirements of the infant are approximately five times greater than those of the adult (1), it is as yet not known whether the high nitrogen requirements of the infant are created by a proportionate increase in all of the amino acids or by a limiting effect caused by higher demands of the growing organism for one or several of the amino acids. The need for an answer to this question, which is of obvious importance to practical infant nutrition and the physiology of growth in general, prompted us to undertake investigations on the amino acid requirements of the infant. The studies reported here reveal that on the basis of nitrogen retention data, rate of weight gain and blood protein levels, the infant requires 5 times more tryptophane per kilo of body weight than does the adult (2). We were surprised to note that within 10 days the tryptophane deficient diet caused a marked hypoproteinaemia in the infant whereas our previous studies had shown that the blood proteins of the adult were unaffected by administration of a tryptophane deficient diet for 6 weeks (3).

EXPERIMENTAL

Procedures. The observations reported here were made on 3 normal healthy white male infants. They were given the experimental diets in 5 feedings daily at the rate of about 100 calories per kilo of body weight which were supplemented with 50 mg. of ascorbic acid and 15 drops of oleum percomorpheum per diem. The diet periods were consecutive and varied in duration from 3 to 7 days, but collec-

¹ The work described in this report was supported by grants from the Rockefeller Foundation, National Live Stock and Meat Board and the Nutrition Foundation, Inc.

tions of the excreta were omitted on week ends to avoid complications which might arise from continued use of restraints. The subjects were immobilized by the use of abdominal restraints. 24-hour urine specimens were collected by means of adapters in bottles containing 10 cc. of 15 per cent (by volume) HCl and 1 cc. of 10 per cent alcoholic thymol and the feces collected in 19 cm. porcelain evaporating dishes held in place by a properly shaped excavation in the mattress and subsequently accumulated under refrigeration for the period in jars containing 200 cc. of 70 per cent alcohol. The infants were weighed daily during the course of the experiment.

The composition of the diets employed is shown in Table I. These were made to contain approximately 100 calories per 100 gm. and have the following percentile caloric distribution: protein, 14; fats, 36; carbohydrate, 50. The protein moiety of the tryptophane deficient diet (TH) was prepared by sulfuric acid hydrolysis of casein as previously described by us (4). In order to improve the cystine-poor characteristic of this preparation, the final product was reinforced with 1 per cent *l*(-)-cystine of the protein content estimated as $N \times 6.25$. The protein component of the control diet (CTH) was similarly derived and then supplemented with 1.5 per cent of *l*(-)-tryptophane. In an attempt to ascertain the minimal tryptophane requirement under these dietary conditions, the tryptophane addition to the diet was made step wise, 0.5 and 1.0 per cent of the protein content and these diets are designated as $\frac{1}{3}$ CTH and $\frac{2}{3}$ CTH respectively. Owing to uncertainties regarding the complete human requirements of B complex vitamins, Brewers' yeast was employed instead of a mixture of the synthetically available vitamins. The quantities of tryptophane derived from this source appear to be approximately 6 mg. per gram (5). Thus the amount of tryptophane provided by the diets per kilogram of infant body weight can be roughly estimated (Table I). The final nitrogen content of each batch of diet was determined by micro-Kjeldahl analysis.

Data on the nitrogen retention were calculated from the results of micro-Kjeldahl analyses of the daily 24 hour urine collections, period pools of feces and daily N intake computed from the consumption record and nitrogen content of diet.

Pooled specimens of urines representative of each diet period

were analyzed for 10 amino acids and other metabolites by methods described by others and ourselves. Since urinary tryptophane undergoes destruction on standing even at refrigerator temperatures, this amino acid was determined in the daily samples (6) and the daily values averaged for each period.

Blood samples (10 cc.) were collected over lithium oxalate on the last day of each period by vena puncture. The hemoglobin content of these specimens was determined colorimetrically in the Klett-

TABLE I
Composition of Diets

DIETS	TH	‡ CTH	‡ CTH	CTH
	gm.	gm.	gm.	gm.
Acid hydrolyzed casein*.....	3.5	3.5	3.4	3.4
l(-)-Tryptophane.....		0.017	0.034	0.053
l(-)-Cystine.....	0.035	0.035	0.035	0.035
Brewers' yeast†.....	1.0	1.0	1.0	1.0
Olive oil.....	4.0	4.0	4.0	4.0
Dextri-maltose #2†.....	9.6	9.6	9.6	9.6
Arrowroot starch.....	2.3	2.3	2.3	2.3
Salt mixture‡.....	1.6	1.6	1.6	1.6
Water.....	78.0	78.0	78.0	78.0
Total.....	100.0	100.0	100.0	100.0
Estimated tryptophane content, mg.....	6	23	40	59

* N x 6.25 = gm. of protein.

† Kindly supplied by the Mead Johnson and Company.

‡ The salt mixture employed had the following composition (measured in gm.): FeSO₄ 0.9, NaCl 6, Ca gluconate 48, Ca(OH)₂ 12, KH₂PO₄ 20, K₂HPO₄ 7, KCl 6, MgO 0.1.

Summerson photoelectric colorimeter. The total plasma proteins, albumin and non-protein N were determined by the usual procedures (7). The globulin was estimated as the difference of total protein and albumin. The amino N content of the plasma was determined by the copper method (8).

RESULTS

The data collected in Table II show that in the absence of dietary tryptophane all three subjects underwent a marked decrease in

the daily weight gain and a drop in nitrogen retention. Since the growing organism is normally in a state of high positive nitrogen balance a drop from the nitrogen retention values characteristic of the individual must be given the same interpretation as the inducement of a negative nitrogen balance in the adult, namely that tryptophane must be regarded as a dietary essential for the infant. This inference is corroborated by the concomitant decrease in body weight gain

TABLE II

Effect of Dietary Tryptophane on the Nitrogen Retention and Body Weight Gain of the Infant

INITIAL AGE AND WEIGHT OF SUBJECT	DIET	PERIOD	AVER- AGE DAILY WT. GAIN	INTAKE PER KG.		TOTAL NITROGEN INPUT	NITROGEN OUTPUT			NITROGEN RETEN- TION
				Vol- ume	Nitro- gen		Urine	Feces	Total	
		days	gm.	cc.	gm.	gm.	gm.	gm.	gm.	mg./kg.
R. D., male 6 mos. 7.281 kg.	CTH	7	16.0	102	0.69	5.01	3.33	0.63	3.96	145
	TH	7	2.1	104	0.64	4.63	3.28	0.53	3.81	110
	TH	4	-39	68	0.53	3.24	3.06	0.19	3.25	-1
	CTH	7	79	109	0.68	4.82	1.61	0.40	2.01	380
D. P., male 7 mos. 7.136 kg.	CTH	7	12.0	100.2	0.69	4.96	3.46	0.47	3.93	144
	TH	7	2.1	103.2	0.64	4.57	3.45	0.28	3.73	101
	TH	4	-32.0	77.5	0.53	3.77	3.37	0.37	3.74	4
	CTH	3	104.0	105.9	0.67	4.80	1.90	0.49	2.39	334
	CTH	4	50.6	102.1	0.67	4.92	3.35	0.55	3.90	135
S. A., male 12 mos. 10.262 kg.	CTH	7	19.9	103	0.65	6.65	4.43	0.88	5.31	130
	TH	7	4.0	98	0.66	6.50	4.45	0.82	5.27	129
	TH	7	-18.1	82	0.51	5.15	4.17	0.39	4.56	57
	$\frac{1}{3}$ CTH	4	-54.3	80	0.45	4.51	2.99	0.90	3.89	59
	$\frac{2}{3}$ CTH	3	66.0	98	0.52	5.29	2.97	0.36	3.33	169
	CTH	4	22.8	99	0.60	6.19	3.71	0.49	4.20	194

caused by the tryptophane deficient diet and the restoration of both growth functions to the norm on the CTH-diet. Incidentally, it is to be noted that in every instance the decrease in weight gain preceded the drop in nitrogen retention.

Attention is also called to the fact that due to the onset of a persistent anorexia in the second TH diet period, the total daily nitrogen intake fell about 1 gram in all three subjects. This anorexia disappeared dramatically with the addition of tryptophane to the diet.

It might therefore be inferred that the drop in nitrogen retention was associated by the decreased intake. However, this does not appear to be the case, since we and others before us (1) have observed that infants of this age are able to retain upwards of 120 mg. of nitrogen per kilogram on intakes of 3.0 gm. of nitrogen derived from milk protein preparations. Further evidence of this phenomenon is to be derived from the data on subject S. A., who retained 169 mg. of N per kilo on an intake of 5.29 gm. of N from $\frac{2}{3}$ CTH diet but retained only 57 mg. of N per kilo of 5.15 gm. of N from TH diet.

Further examination of these data reveals that feeding of CTH diet to subjects R. D. and D. P. following the 11 days of tryptophane poor diet causes an abnormally high nitrogen retention and weight gain which returned to normal levels in the second week of CTH diet (subject D. P.). Inasmuch as this did not occur in subject S. A. who was given the $\frac{1}{3}$ CTH and $\frac{2}{3}$ CTH diets prior to the CTH, suggests that a vigorous and compensatory resumption of growth under a limited tryptophane intake is only possible when the full complement was made available to the organism.

Inasmuch as diets TH and CTH furnish respectively about 6 and 59 mg. of tryptophane per kilo of body weight, the tryptophane requirement of the infant must lie between these two limits. In the single experiment (S. A.) in which the tryptophane content of the diet was increased stepwise, it was found that unlike the $\frac{1}{3}$ CTH diet, the $\frac{2}{3}$ CTH caused a return of both growth functions to the norm. This finding suggests that under the dietary conditions of these studies, the tryptophane requirement of the infant is between 23 and 40 mg. per kilo, or approximately 15 times the adult need.

The implications of the nitrogen balance measurements appear to be supported by variations in urinary tryptophane output induced by the various diets (Table III). Thus it will be noted that in all subjects the tryptophane output falls below the normal of each individual with the removal of tryptophane from the diet and returns to the norm on restoration of tryptophane to the diet. Interestingly enough, the upsurge in urinary tryptophane occurred during the $\frac{2}{3}$ CTH diet and not in the $\frac{1}{3}$ CTH diet period. These findings lend additional support to the notion that the tryptophane level of the urine may serve as a criterion for the estimation of the minimum dietary requirement of the amino acid.

Measurements of the blood proteins during the various regimens disclosed that within 10 days a tryptophane-poor diet caused an

TABLE III

*Effect of Dietary Tryptophane on the Daily Urinary Tryptophane Output of the Infant**

R. D., MALE, 5 MO., 7.28 KG.			D. P., MALE, 7 MO., 7.14 KG.			S. A., MALE, 12 MO., 10.26 KG.		
Diet	Period	Trypto- phane	Diet	Period	Trypto- phane	Diet	Period	Trypto- phane
	days	gm.		days	mg.		days	mg.
CTH	7	27	CTH	7	24	CTH	7	58
TH	7	20	TH	7	26	TH	7	47
TH	4	14	TH	4	12	TH	7	31
CTH	7	20	CTH	3	10	$\frac{1}{2}$ CTH	4	16
			CTH	4	32	$\frac{3}{4}$ CTH	3	31
						CTH	4	54

* Unlike the microbiological procedures the chemical procedure (6) employed in this work measures the total (free and bound) tryptophane output.

TABLE IV

Effect of Dietary Tryptophane on the Blood Proteins of the Infant

SUBJECT	DIET	PERIOD	TOTAL PLASMA PRO- TEINS	ALBU- MIN	GLOBU- LIN	A/G RATIO	NON- PROTEIN NITRO- GEN	HEMO- GLOBIN	AMINO NITRO- GEN
		days	gm. %	gm. %	gm. %		mg. %	gm. %	mg. %
R. D., male 5 mos. 7,281 gm.	CTH	7	5.88	3.78	2.10	1.80	30.3	9.7	7.7
	TH	7	5.35	3.54	1.81	1.96	29.6	10.5	8.1
	TH	4	4.88	3.32	1.56	2.13	24.3	10.4	8.1
	CTH	7	5.54	3.58	1.96	1.96	17.9	9.7	7.9
D. P., male 7 mos. 7,136 gm.	CTH	7	5.64	4.05	1.59	2.54	28.9	8.4	8.1
	TH	7	4.68	2.92	1.76	1.66	25.7	9.1	9.4
	TH	4	4.32	2.82	1.50	1.88	27.7	9.2	9.9
	CTH	3	—	—	—	—	—	—	—
	CTH	4	5.96	3.82	1.73	2.21	16.2	9.1	8.7
S. A., male 12 mos. 10,262 gm.	CTH	7	5.88	3.41	2.47	1.38	29.1	8.5	7.0
	TH	7	5.13	3.03	2.10	1.44	29.8	8.5	8.5
	TH	7	4.28	2.80	1.48	1.89	30.9	10.2	8.4
	$\frac{1}{2}$ CTH	4	5.69	3.02	2.67	1.13	17.8	10.0	8.1
	$\frac{3}{4}$ CTH	3	5.53	3.04	2.49	1.22	23.4	10.5	8.4
	CTH	4	5.93	2.99	2.94	1.02	20.6	10.7	8.1

appreciable hypoproteinemia which is reflected for the most part in a decreased albumin level (Table IV). Attention is called to the

finding in subject S. A., where the nitrogen retention, weight change and urinary tryptophane values became normal during the $\frac{2}{3}$ CTH diet period, while the plasma proteins were returned to nearly normal levels by the $\frac{1}{3}$ CTH diet. This observation suggests to us that the blood proteins have a higher priority on the available nutrients than other body tissues. The hemoglobin concentration and amino N level of the blood do not appear to be influenced by the brief period of tryptophane deficiency. Cell counts remained within normal levels at all times during the course of the studies.

COMMENTS

We have previously reported that on the basis of nitrogen balance and urinary tryptophane data, the tryptophane requirement of the adult was approximately 6 mg. per kilogram of body weight (2). In the present study measurements of nitrogen retention, rate of body weight gain, urinary tryptophane output and plasma protein levels indicate that infants 5 to 12 months of age require about 30 mg. of *l*(-)-tryptophane per kilo of body weight for normal growth. It appears, therefore, that on a weight basis, the tryptophane, like the nitrogen needs of the infant are five times as great as those of the adult and that the high protein requirement of the infant is predicated in part by the tryptophane needs. In our studies on the effect of an experimental tryptophane deficient diet in the adult (3) we observed that the plasma proteins failed to reflect the dietary defect even after six weeks of the regimen. This result is to be contrasted with the rapid drop of plasma protein levels induced in the infant by the tryptophane poor diet. A reaction, indeed, more rapid than that observed in the immature or adult rat (4). This phenomenon cannot but impress one of the relatively greater biological sensitivity of the infant to dietary privations and of the desirability of measuring the nutritional requirements of the infant directly rather than upon inferences derived from results of adult human or rat experiments.

The pronounced anorexia which all three subjects developed to the tryptophane deficient diet and its disappearance on supplementation of the deficient diet with *l*(-)-tryptophane arouses considerable speculation as to its etiology. The infants' dislike for the deficient diet cannot reasonably be attributed to a difference in taste of the

two preparations, since the addition of the necessary but small amount of tryptophane could not be expected to greatly improve the taste of the preparation; and indeed a change in taste could not be detected by us. Apparently, the symptom is caused by the same psychological factors which regulate self-selection of diets in experimental animals (9) which have also been shown to function in the child (10).

SUMMARY

It has been found that the infant requires approximately 30 mg. of *l*(-)-tryptophane per kilogram of body weight per day for the maintenance of normal growth, nitrogen retention and plasma protein levels. The significance of these findings is discussed.

We wish to thank Mrs. Barbara Saur for some analyses performed in connection with this work.

BIBLIOGRAPHY

1. ALBANESE, A. A.: The amino acid requirements of the human, in *Advances in Protein Chemistry*. New York, Vol. III, pp. 227-268 (1946).
2. HOLT, L. E., ALBANESE, A. A., FRANKSTON, J. E., AND IRBY, V.: *Bull. Johns Hopkins Hospital*, 75: 353 (1944).
3. HOLT, L. E. JR., ALBANESE, A. A., BRUMBACK, J. E., JR., KAJDI, C., AND WANGERIN, D. M.: *Proc. Soc. Exp. Biol. and Med.*, 48: 726 (1941).
4. ALBANESE, A. A., HOLT, L. E., JR., KAJDI, C. N., AND FRANKSTON, J. E.: *Biol. Chem.*, 148: 299 (1943).
5. CARTER, H. E., AND PHILLIPS, G. E.: *Fed. Proc.*, 3: 123 (1944).
6. ALBANESE, A. A., AND FRANKSTON, J. E.: *J. Biol. Chem.*, 157: 59 (1945).
7. ROBINSON, H. W., PRICE, J. W., AND HOGDEN, C. G.: *J. Biol. Chem.*, 120: 481 (1937).
8. ALBANESE, A. A., AND IRBY, V.: *J. Biol. Chem.*, 153: 583 (1944).
9. RICHTER, C. P.: *The Self-Selection of Diets. Essays in Biology*, 501-506 U. of Calif. press 1943.
10. SWEET, C.: *J. A. M. A.*, 107: 765 (1936).
DAVIS, C. M.: *Am. J. D. C.*, 36: 651 (1928); 46: 743 (1933).

THE ANTIPELLAGRA ACTION OF N¹-METHYLNICOTINAMIDE¹

VICTOR A. NAJJAR AND CAROLYN C. DEAL

From the Department of Pediatrics, Johns Hopkins Medical School and The Harriet Lane Home, Johns Hopkins Hospital, Baltimore, Maryland

It is now generally accepted that the F₂ product (1, 2, 3) of nicotinamide metabolism is mostly and N¹-methylnicotinamide compound (4, 5, 6, 7). In studying the biological activity of this compound Najjar et al. (8) showed that dogs placed on a black tongue producing diet and receiving N¹-methylnicotinamide chloride as a supplement did not develop symptoms and signs of nicotinic acid deficiency, whereas the controls, animals not receiving the drug, developed the disease. With large doses of N¹-methylnicotinamide, one dog with manifest deficiency showed a good curative response. This was not substantiated by the work of Teply et al. (9). However, Vance (10) was able to effect cure in a case of human pellagra, using large doses of the drug.

A comparative study of the vitamin effect of nicotinamide and its methyl derivative was carried out. The results, shown below, indicate that the methyl derivative showed some response but far less pronounced than that of nicotinamide. The positive response is further proof that the drug does not display a vitamin analogue effect (11), similar to that obtained by Wooley (13) using 3-acetylpyridine as a vitamin analogue that precipitated nicotinic acid deficiency in mice.

EXPERIMENTAL

Three young male dogs were used, weighing 6.0, 8.3 and 8.4 kilograms. These were housed in individual cages, weighed daily and fed unlimited quantities of a black tongue producing diet supplemented with thiamin and riboflavin (8). When their weights declined, appetites began to fail and before any manifest deficiency symptoms were apparent, the animals received by intramuscular injection equimolar quantities of the vitamin or its methyl derivative and the re-

¹ Aided by a grant from Mead Johnson and Company, Evansville, Indiana.

sponse was observed. 0.5 mg. of nicotinamide or 0.707 mg. of N¹-methylnicotinamide chloride² per kilogram of body weight were administered daily for a period of ten days. The parenteral route

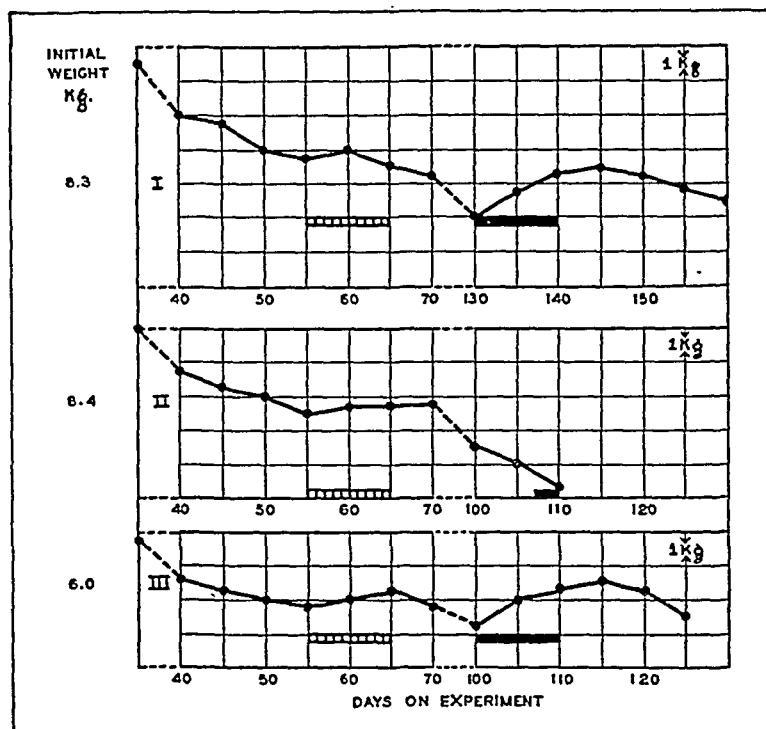


FIG. 1. □□□ = N¹-methylnicotinamide chloride injected—0.707 mg. per kilogram. ■■■ = Nicotinamide injected—0.5 mg. per kilogram.

The break in the curves indicates a period where no therapy was given. Dog I, however, was given a second treatment with N¹-methylnicotinamide for ten days on the 100th day. The response was similar to that shown on the curve.

thus used precludes the possibility of any conversion of the methyl compound to nicotinamide by bacterial action or otherwise.

² The N¹-methylnicotinamide chloride was prepared by Karrer's method (12). Its melting point and that of its picrate were obtained essentially as in the previous report (8).

With the purity of the material as checked by the melting point, any possible contamination with nicotinamide would be chemically negligible and, with the small doses used, biologically not detectable.

Two of the dogs treated with nicotinamide showed a marked improvement in appetite and a striking gain in weight which was maintained for over five days after the last dose was given. Dog II, however, died suddenly on the third day of therapy which explains its failure to respond. No demonstrable cause was found at autopsy.

N¹-methylnicotinamide chloride, however, produced only a slight improvement in appetite and, at best, a slight gain in weight or a cessation in weight loss, neither of which were sustained beyond the last day of therapy.

CONCLUSION

N¹-methylnicotinamide chloride has a slight antipellagra effect, although much less pronounced than nicotinamide on an equimolar basis.

BIBLIOGRAPHY

- (1) NAJJAR, V. A., AND WOOD, R. W., *Proc. Soc. Exper. Biol. and Med.*, **44**: 386, 1940.
- (2) NAJJAR, V. A., AND HOLT, L. E., JR., *Science*, **93**: 20, 1941.
- (3) NAJJAR, V. A., AND HOLT, L. E., JR., *Proc. Soc. Exper. Biol. and Med.*, **48**: 413, 1941.
- (4) HUFF, J. W., AND PERLZWEIG, W. A., *J. Biol. Chem.*, **150**: 395, 1943.
- (5) ELLINGER, P., AND COULSON, R. A., *Nature*, **152**: 383, 1943.
- (6) SARRETT, H. P., *J. Biol. Chem.*, **150**: 159, 1943.
- (7) NAJJAR, V. A., WHITE, V., AND SCOTT, D. B. M., *Bull. Johns Hopkins Hosp.*, **74**: 378, 1944.
- (8) NAJJAR, V. A., HAMMOND, M. M., ENGLISH, M. A., WOODEN, M. B., AND DEAL, C. C. *Bull. John Hopkins Hosp.*, **74**: 406, 1944.
- (9) TEPLY, L. J., KREHL, W. A., AND ELVEHJEM, C. A., *Proc. Soc. Exper. Biol. and Med.*, **58**: 169, 1945.
- (10) VANCE, G. A., *Bull. Johns Hopkins Hosp.*, **77**: 393, 1945.
- (11) NAJJAR, V. A., AND RATCLIFFE, I. M., in press.
- (12) KARRER, P., SCHWARTZENBACH, G., BENZ, F., AND SOLLMSSEN, U., *Helv. Chim. Acta.*, **19**: 811, 1936.
- (13) WOOLEY, D. W., *J. Biol. Chem.*, **157**: 455, 1945.

DISAPPEARANCE TIME OF TREPONEMA PALLIDUM FROM LESIONS OF EARLY SYPHILIS FOLLOWING ADMINISTRATION OF CRYSTALLINE PENICILLIN G¹

HAROLD A. TUCKER, M.D. AND RAYMOND C. V. ROBINSON, M.D.

From the Syphilis Division of the Medical Department, The Johns Hopkins University

When the sodium salt of crystalline penicillin G became available for research purposes it was necessary to establish the potency of the new preparation in syphilitic infections in man. Several methods of assay have been employed, including determinations of blood levels and urinary excretion, but none has been entirely satisfactory. One recent report (1) deals with the effect of single intramuscular injections of penicillin G and related species of penicillins on darkfield positive syphilitic lesions in man. No attempt was made, however, to determine a quantitative relationship between dosage and disappearance time of surface *Treponema pallida*.

In this communication we report the results of a serial darkfield method in 35 patients with early syphilis. The sodium salt of penicillin G was administered to each on a gravimetric basis and darkfield examinations for *T. pallidum* were done at intervals during the following 48 hours in order to ascertain the effect on surface treponemes of various dosages of the antibiotic agent.

MATERIAL AND METHODS

Patients used in this study all had darkfield positive cutaneous or mucocutaneous lesions of primary and/or secondary syphilis. None had received previous treatment of any kind for the present syphilitic infection and all were hospitalized throughout the period of observation. The lesions chosen were early and succulent, usually measuring

¹ This work was done under a contract recommended by the Committee of Medical Research between the Office of Scientific Research and Development and The Johns Hopkins University; and under a grant-in-aid to the Johns Hopkins University from the United States Public Health Service, National Institute of Health, Syphilis Study Section.

Penicillin fractions employed were furnished by Dr. Harry Eagle.

TABLE 1

Duration of Darkfield Positivity in Lesions of Early Syphilis in Man Following Varying Dosages of Penicillin G

TOTAL DOSE	OXFORD UNITS	NUMBER OF PATIENTS TESTED	NUMBER DARKFIELD POSITIVE AT HOURS					
			6	9	13	18	24	48
<i>mg./kg.</i>	<i>u./kg.</i>							
87.0	130,500	1	1	0	0	0	0	0
15.0	22,500	2	2	2	0	0	0	0
3.00	4,500	1	1	1	0	0	0	0
0.600	1,000	2	2	2	0	0	0	0
0.180	300	3	3	3	0	0	0	0
0.090	150	6	6	6	3	1	0	0
0.075	125	5	5	5	3	1	1	0
0.060	100	9	9	9	6	5	3	1
0.053	88	4	4	4	4	3	4	3
0.038	64	2	2	2	2	2	2	2

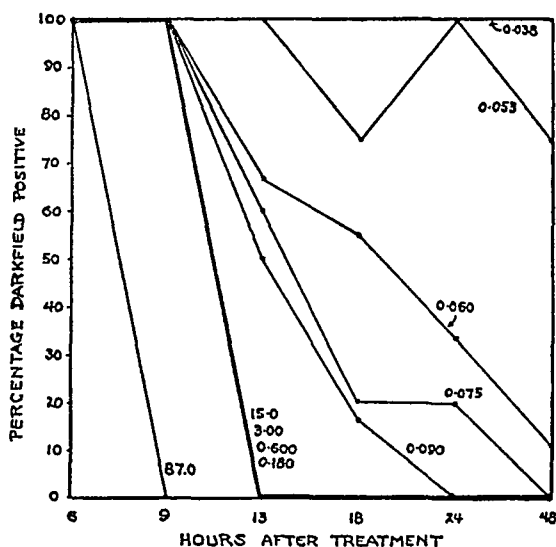


FIG. 1. GRAPH SHOWING PERCENTAGE OF PATIENTS REMAINING DARKFIELD POSITIVE AT INTERVALS FOLLOWING GRAVIMETRIC ADMINISTRATION OF PENICILLIN G

over 1 cm. in diameter and, where several were present, an effort was made to utilize the same one for all tests.

The method employed was as follows: the lesion selected was abraded 2 or 3 times, after removal of crusts, and firmly squeezed until abundant clear serum was seen. Serum obtained was examined at once for treponemes and negative results were checked by a second observer. Examinations were called negative only after a 10 to 15 minute search on each of 2 or more preparations. The patients receiving the smallest amount of penicillin served as controls for the method itself, in that their lesions remained positive throughout the observation period.

The total dosage was calculated on a gravimetric basis in terms of body weight and was administered in 3 equal intramuscular injections in aqueous solution at intervals of three hours. At the time of the third injection the six-hour darkfield examination was performed. In the 4 patients receiving the largest dosages, a preparation was employed which contained over 1500 Oxford units per mg. of penicillin G (Commercial Solvents Corporation 46042605). All others were given the pure crystalline product having an *in vitro* potency against the standard test strain of *Staphylococcus aureus* of 1667 units per mg. (Merck 1116).

RESULTS

Results of these studies are presented in Table 1. It is apparent that an inverse relationship exists between the dosage of the antibiotic and the time required for disappearance of surface treponemes. Variability among members of groups receiving the smallest dosages is also noteworthy. Figure 1 shows the relations of the 3 factors considered: dosage, time and darkfield positivity.

Febrile or febrile and cutaneous Herxheimer reactions occurred in more than half the patients studied.

DISCUSSION

Although lesions are reported to have become darkfield negative 3 hours after the administration of intramuscular commercial penicillin (2), we failed to obtain negativity in less than 6 hours even when a total dosage approximating 6,250,000 Oxford units was used. According to Olansky and Putnam (1) 6 of their patients were darkfield negative

8 hours after a single dose of 50,000 Oxford units of penicillin G (30 mg.); the mean time for all 10 patients was 9.6 hours. These data, together with the marked variation found in our material where a standardized darkfield method was employed, demonstrate the impracticability of such procedures in the assay of penicillin preparations in man.

Within the range studied, the severity and duration of Herxheimer reactions appeared to be unrelated to the dosage of penicillin G employed. For example, the patient receiving 87.0 mg./kg. of the antibiotic had no Herxheimer reaction, whereas a majority of those who got the smaller amounts had febrile responses.

Too few patients have as yet been studied in a similar manner with other species of penicillins to warrant conclusions.²

The effect of penicillin G on surface treponemes in rabbit syphilis is under investigation by Turner and his associates (3). A comparison of data disclosed that the amount of penicillin required to produce an endpoint at 24 hours was of the same general order of magnitude (approximately 0.060 mg./kg. for rabbits, approximately 0.075 mg./kg. for man), under the conditions of the 2 experiments. Endpoints differed in that we required negativity; Turner and his associates, however, required only that the number of *T. pallida* be reduced by 95 per cent or more from an original count of 100 organisms or greater.

SUMMARY

Thirty-five patients with early syphilis were given penicillin G in amounts ranging from 0.038 to 87.0 mg./kg.; darkfield examinations were then done at intervals. An inverse relationship between dosage of penicillin G and time required for disappearance of surface trep-

² A total of 0.50 mg./kg. (20,000 units intramuscularly every 3 hours for 3 doses) and 0.33 mg./kg. (20,000 every 3 hours for 2 injections) of penicillin K were given to each of 2 patients. In the first, darkfield examination was positive at 15.5, negative at 24 hours, while in the second patient, examination was positive at 12, negative at 15.5 hours.

Another patient was given a total of 0.60 mg./kg. of penicillin X in a single dose. Darkfield examination at 16 hours was positive but no *T. pallida* were seen at 24 hours.

onemes was demonstrated. Variability among patients receiving comparable dosages was so great as to make the method unsatisfactory for the assay of penicillin preparations in man.

REFERENCES

1. OLANSKY, S., AND PUTNAM, L. E.: The Effect of the Sodium Salts of Crystalline Penicillin G, Crystalline Penicillin X, and Commercial Penicillins on Dark-field Positive Lesions of Syphilis. *J. Ven. Dis. Inform.*, **27**: 178, 1946.
2. LEIFER, W.: Treatment of Early Syphilis with Penicillin. *J. A. M. A.*, **129**: 1247, 1945.
3. TURNER, T. B., CUMBERLAND, M. C., AND LI, H. L.: Personal communication.

THE PREVENTION OF PYLORIC LIGATION-INDUCED ULCERS OF THE GASTRIC RUMEN OF RATS BY TRANS-ABDOMINAL VAGOTOMY: A PRELIMINARY REPORT

HENRY N. HARKINS, M.D.

From the Department of Surgery, Johns Hopkins University and the Johns Hopkins Hospital

Starved rats regularly develop multiple hemorrhagic ulcerations of the gastric rumen, as well as occasional ulcers of the gastric fundus, within 15 hours following pyloric ligation. This phenomenon, first observed by Shay, Komerov, Fels, and Meranze (1945) and further studied by Pauls, Wick and MacKay (1946) was regularly seen in our control rats. It was thought advisable to test the effect of vagotomy on the development of these ulcerations.

Technic: Littermate albino rats of the Sprague-Dawley strain weighing about 200 gms. were starved for 72 hours. The animals were allowed water ad libitum and were placed in cages with wide mesh wire bottoms to eliminate eating of excreta. The animals were then anesthetized with intraperitoneal pentothal plus inhalation ether. Using aseptic precautions, a short vertical epigastric incision was made to expose the stomach. The pylorus was ligated in all animals, and in the vagotomized half of the series, the vagus nerves were completely and tightly ligated just below the diaphragm. In the control series, the esophagus was freed from the surrounding nerves exactly as for vagotomy, except that the vagi were not ligated. The abdominal wound was then resutured, the animals were replaced in the cages this time without water, and either killed with ether at the end of a specified time, or permitted to live until death in the survival experiments.

Results: (a) *Animals killed at the end of 24 hours.* In the control series all of the 22 rats had ulcerations of the gastric rumen and 8 out of 22 had ulcers in the fundus. The average number of ulcers in the rumen was 22 per rat, as shown in Table 1. There were 435 small ulcers and 45 large ulcers, the latter being by definition larger than 4 mm. in one diameter. Two of the rats had a perforated ulcer of the rumen. In the 20 vagotomized rats there were no ulcers of the

rumen or fundus in any instance. Microscopically, the ulcers were deep, as described by Shay, et al., and involved most of the layers of the stomach wall. There was considerable edema of the stomach wall in the ulcerated control series. The vagotomized stomachs showed no microscopic edema or ulceration.

As also seen in Table 1, the control animals had much more fluid in the stomach at death than did the vagotomized rats (15 cc. as opposed to 7 cc.). Furthermore, the gastric fluid was more acid in

TABLE 1

The Effect of Vagotomy on the Development of Ulcers of the Gastric Rumen of the Rat Twenty-Four Hours After Pyloric Ligation

	22 CONTROL RATS	20 VAGOTOMIZED RATS
Small ulcers.....	435	0
Large ulcers (>4 mm.).....	45	0
Ulcers of rumen (av. per rat).....	22	0
Perforations of ulcers.....	2	0
Ulcer of fundus present.....	8	0
Volume gastric fluid average (cc.).....	15	7
Free acid average (units).....	34	8
Total acid average (units).....	94	66

TABLE 2

The Effect of Vagotomy on the Duration of Life in Rats After Pyloric Ligation

	10 CONTROL RATS	10 VAGOTOMIZED RATS
Average length of life in hours.....	49	106

the control series (free acid = 34 average; total acid = 94 average), than that from the vagotomized stomachs (free acid = 8 average; total acid = 66 average).

(b) *Survival experiments.* A series of 20 rats was treated by pyloric ligation and half were in addition vagotomized. The animals received almost daily intraperitoneal glucose-saline injections to prevent dehydration. As shown in Table 2, the ten control animals lived an average of 49 hours while the equal number of rats with supplementary vagotomy lived an average of 106 hours. In every pair of rats the vagotomized animal lived the longest.

Discussion: Whether the lesions usually produced by pyloric ligation can be classified as ulcers or erosions, the fact remains that vagotomy completely inhibited their development in the series studied and over the time limit of 24 hours utilized in these experiments. The mode of action of vagotomy is not entirely clear. A lessened gastric acidity is not the only factor, because certain control rats developed ulcers despite a less acid gastric juice than observed in some of the vagotomized rats, none of which showed ulcerations. A lessened gastric distension is also not the only factor, because certain control rats developed ulcers despite a smaller amount of gastric contents than observed in some of the vagotomized rats, none of which, as was pointed out before, showed ulcerations.

CONCLUSIONS

1. The production by pyloric ligation of ulcerations of the gastric rumen in starved rats has been prevented in the experiments outlined above by transabdominal vagotomy (Control series = 480 ulcers in 22 rats; vagotomized series = 0 ulcers in 20 rats).
2. Vagotomy lengthens the life of pylorus-ligated rats under the conditions studied (Control series = 49 hours average; vagotomized series = 106 hours average).
3. Vagotomy lessens the acidity and volume of the accumulated gastric fluid, but neither of these factors alone explains the prevention of the ulcerations by this procedure.

The gastric analyses were done by Mr. Stuart R. Elliott, II.

BIBLIOGRAPHY

1. PAULS, F., WICK, A. N., AND MACKEY, E. M.: Use of Shay Rat for Assay of Antiulcer Substances. *Science* 103: 673 (May 31) 1946.
2. SHAY, H., KOMEROV, S. A., FELS, S. S., MERANZE, D., GRUENSTEIN, M., AND SIPLET, H.: A Simple Method For the Uniform Production of Gastric Ulceration in the Rat. *Gastroent.* 5: 43-61 (July) 1945.

BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of this Journal)

Psychotherapy in General Medicine: Report of an Experimental Postgraduate Course.
By GEDDES SMITH. 38 pp. \$.25. *The Commonwealth Fund, New York, New York, 1946.*

Increasing recognition of the importance of basic psychiatric principles and methods in general medical practice has stimulated educational planning to overcome past deficiencies. This booklet of 38 pages sets forth succinctly a pioneer experience in attempting to teach psychotherapy to 25 general practitioners in Minnesota in a two weeks course, sponsored by the Commonwealth Fund and the Division of Postgraduate Education of the University of Minnesota. This account of the experiential project high-lights the vivid personal and emotional experience of the practitioner-students in this concentrated training in which the main theoretical emphasis was placed on understanding personality development, and the meaningfulness of symptoms, and the main practical emphasis was placed on the doctor's opportunity to influence personality functions through an understanding use of the emotions and dynamics of the doctor-patient relationship. A follow-up study is planned.

In the reviewer's opinion, this educational experiment is an expression of a vital change in the role of psychiatry in medical education, and it may light the way to more effective means of teaching basic psychiatry at graduate and undergraduate levels.

J. C. W.

Jerome Cardan. By JAMES ECKMAN. 120 pp. \$2.00. Supplements to the Bulletin of the History of Medicine, No. 7. *The Johns Hopkins Press, Baltimore, Maryland, 1946.*

Stimulated by previous study of the period of the Renaissance, James Eckman has written "Jerome Cardan" to signalize the quatercentenary of Cardan's "Ars Magna" and to enliven the waning fame of that physician and mathematician of the sixteenth century. The present work is a scholarly one in which the author attempts to appraise his subject in terms of the writings of his contemporary and later critics, friendly and hostile, as well as in the light of Cardan's own writings. In his examination of the literature concerning Cardan, the author has made also the interesting discovery that "The Life and Times of Jerome Cardan" by James Crossley is apparently an apochryphal biography. Because of the extensive annotation, this biographical monograph is somewhat lacking in narrative quality and is more likely to appeal to the serious student of medical history than to the casual reader thereof.

R. A.

A Primer for Diabetic Patients. By RUSSELL M. WILDER. 8th Ed. Illus. 192 pp. \$1.75. W. B. Saunders Company, Philadelphia, Pennsylvania, 1946.

Designed to help the diabetic patient understand his disease and many of the principles underlying the treatment of diabetes, this book has been of tremendous assistance to the medical profession since its first edition in 1921. It covers in simple terms the physiology of diabetes, gives instructions for assaying urine sugar and ketone bodies, discusses the dosage and administration of insulin, the treatment of complications, and the principles of diet with many recipes and lists of substitution equivalents.

The 8th edition contains several changes from the 7th issued in 1941, the most important of which is in the section on the use of insulin. This edition requires the patient to adjust his insulin so that the urine will be free of sugar, whereas earlier editions permitted the spilling of some sugar provided there were no symptoms or ketonuria.

There will be some criticism of this book because it could encourage self treatment by independent patients, and because the diets outlined tend to have more fat and less carbohydrate than some clinics recommend. But used as an adjunct to adequate medical supervision it will continue to be one of the most useful and practical guides for diabetics.

R. E. M.

Surgery of Repair-Injuries and Burns. By D. N. MATTHEWS. Illus. 386 pp. \$10.00. Charles C Thomas, Springfield, Illinois, 1943.

The material in this book is based upon the broad experiences of the author in treating casualties of the Royal Air Force during World War II.

While emphasis is laid on the treatment of injuries which commonly come within the domain of plastic surgery, practically all types of injuries are discussed with the exception of orthopedic and neurosurgical problems. With such a wide range of topics in a relatively small volume it has apparently been necessary to oversimplify and condense some sections of the book.

Certain general principles of treatment which are advocated were widely used at the beginning of the war but were later apparently largely superseded by other forms of therapy. The local use of sulfanilamide which the author frequently advises was seriously questioned and in some theaters largely abandoned. The use of plasma in preference to blood in the treatment of shock in most battle casualties as advocated in this volume might also be questioned. Even in the care of burned patients with marked hemoconcentration the judicious use of whole blood has been recommended by the recent reports of the Shock Committee of the National Research Council. The superiority of whole blood over plasma in shock therapy was repeatedly emphasized in the later years of the war although plasma was generally more readily available.

The "closed" method of treating burns by means of undisturbed vaseline pressure dressings, which is very widely used in this country, is not discussed.

Many of the standard techniques of plastic surgery, free skin grafting, elevation

and transplantation of skin tubes and flaps, and so on, are clearly described and amply illustrated.

As a survey of the field of traumatic surgery the book has definite value, but for one specializing in this field more detailed information can be obtained elsewhere.

W. P. L., Jr.

The Traumatic Deformities and Disabilities of the Upper Extremity. By ARTHUR STEINDLER. Illus. 515 pp. \$10.00. Charles C Thomas, Springfield, Illinois, 1946.

In an interesting book of handy size, the author has succeeded in adequately covering the subject of the disabilities and deformities of the upper extremity resulting from injury. This is accomplished by grouping the changes under the heading of functional disturbances rather than under anatomical divisions. Many of the pathologic changes and therapeutic considerations are assembled into one section that deals with such subjects as contractures of muscles, articular capsules and skin, mechanical principles, and processes of repair of bone, tendon and nerves. This results in appreciable space saving.

The applicable principles of surgery, physiotherapy and occupational therapy are handled in a similar manner. The description of the traumatized structures and the associated functional disturbances are then presented in a comprehensive manner without repetitious discussion of secondary changes.

To get the greatest value from this book, it should first be studied as a whole. After this has been done, references to specific lesions will yield a comprehensive picture in a minimum of time. Numerous illustrations help clarify the text. Case reports give concrete examples of the lesions and the procedures. The listing of numerous references at the end of each section enhances the value of the book. The general surgeon, the traumatologist, and the orthopedist will each find this volume a desirable addition to his library.

W. N.

Diabetic Care in Pictures. By HELEN ROSENTHAL, FRANCES STERN and JOSEPH ROSENTHAL. Illus. 150 pp. \$2.00. J. B. Lippincott Company, Philadelphia, Pennsylvania, 1946.

The idea of teaching the diabetic patient dietetic principles by means of pictures seems to us excellent in principle. The text is written in admirably simple diction, and the pictures are good. There are, however, certain dilemmas presented to the user, which, despite the obvious advantages of the method, are highly confusing. On one page are given protein equivalents, on another carbohydrate and on a third fat. If, for example, one wants to include milk in the diet, he learns on page 24 that one whole cup furnishes 7 grams of protein, on page 40 that $\frac{1}{2}$ cup contains 5 grams of fat and on page 42 that 2 tablespoonsful contain 0.36 grams calcium, etc. This presents a rather nice problem in arithmetic as the amounts of milk differ in each instance.

In the exchanges the method of calculation becomes difficult, too; for example, 3 ounces of mackerel and 4 olives are equable fat exchanges, but what about the protein in the mackerel? This difficulty holds throughout all the exchange food values, and to us seems to make rather complicated confusion out of what is designed to provide simplification. Should the authors manage in another edition to circumvent these dilemmas, the book would be a real contribution and should prove useful to diabetic patients.

J. E. H.

PULMONARY EDEMA AND PLEURAL EFFUSION PRODUCED BY ACUTE ALPHA-NAPHTHYL THIOUREA POISONING IN RATS AND DOGS*

HARRISON LATTAT†

*Psychobiological Laboratory and Department of Pathology
of The Johns Hopkins Medical School*

INTRODUCTION

Previous papers showed that phenyl thiourea produces a marked pulmonary edema and pleural effusion in domestic Norway rats and kills in doses of 1 to 2 mg. per average-sized adult rat (1, 2). Later it was reported that alpha-naphthyl thiourea (subsequently referred to as ANTU) produces the same effects and has the same high toxicity; and that both ANTU and phenyl thiourea produce the same effects on recently trapped wild Norway rats (3). A combination of high toxicity and high acceptance makes ANTU an effective rodenticide. In addition, ANTU provides a means of studying the physiological problems of pulmonary edema and pleural effusion with relative freedom from other factors such as heart failure and pneumonia.

ANTU is toxic also to dogs, killing in doses of as small as 16 mg./kg. intraperitoneally; to mice, killing in doses as low as 50 mg./kg. intraperitoneally; and to domestic pigs, killing in doses as low as 35 mg./kg. by mouth (4, 5). It is less toxic to guinea pigs, Alexandrine rats, and cats, killing in doses of several hundred milligrams per kilogram; and practically nontoxic to rabbits and monkeys, killing only in doses of several grams per kilogram. For dogs, pigs, mice, and cats, it appears to have the same effect on the lungs as it does in the Norway rat. The other animals studied in this laboratory show little or no pulmonary edema or pleural effusion.

The present report gives a detailed account of the changes produced by ANTU poisoning in the lungs and pleural cavities of rats and dogs.

* Started under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and The Johns Hopkins University, and continued under a contract between the Medical Division, Chemical Corps, U. S. Army, and The Johns Hopkins University.

† Formerly of the Department of Pathology, The Johns Hopkins Medical School; now First Lieutenant, M.C., at the Army Institute of Pathology, Washington, D. C.

MATERIAL

Rats. The material consists of several sections of both lungs from each of 17 (5 males and 12 females) adult wild Norway rats, which were trapped in Baltimore in the fall of 1943. A few days after trapping (2-4 days in most instances), ANTU suspended in olive oil was injected intraperitoneally in a dosage of 33 mg./kg. Their weights varied from 256-477 gm. Three of the females were found to be pregnant and one postpartum. The rats were killed, by crushing the cervical spine, at intervals from 1 to 22 hours after injection, except for 3 rats, one of which died at 17½ hours, and the other 2 at 19½ hours. The usual survival time, after doses of this size, was 16 to 22 hours, as determined with several dozen other wild Norway rats. All of the autopsies were performed by one person. Sections were taken from the major organs and other tissues of interest. The tissues were fixed in Zenker-formalin and stained with hematoxylin and eosin. Bacterial stains were made on the lungs of the 5 longest-living rats.

Similar lung sections were prepared from 10 control wild Norway rats trapped at about the same time, and also killed by crushing the cervical vertebrae.

A few chemical and microscopic studies on bronchial and pleural fluid were made on other ANTU-treated wild Norway rats.

Ten domestic Norway albino rats were given ANTU by stomach tube (300 mg./kg. in olive oil) and killed at intervals from 30 minutes to 6 hours by fracturing the cervical vertebrae. Sections from both lungs and from the mediastinum of each animal were made.

Dogs. Fifty-three lung slides from 9 dogs, which died in 12-24 hours after receiving ANTU intraperitoneally in doses ranging from 15.7 mg./kg. to 165 mg./kg., were prepared similarly to the rat lungs. Bacterial stains were made on 3 of the lungs which showed the largest number of polymorphonuclear leukocytes.

Some of the data came from physiological observations that were made by Dr. Cecil Drinker, of the Harvard School of Public Health, on the lymph flow from the lungs and heart of one dog. Also included are the results of an experiment performed by Dr. Richard Bing, of The Johns Hopkins Hospital, on the hemodynamic effects produced by ANTU poisoning in 2 dogs.

RATS

Gross Appearance of Lungs. The striking finding at autopsy is pulmonary edema associated with pleural effusion, both of which are quite marked in the animals allowed to live a longer time after the injection of ANTU. Rats dying from ANTU poisoning are frequently found lying with their nose and mouth in the center of a large pool of fluid from the trachea. Opening the thorax discloses a remarkable sight. The pleural cavities are filled with a large amount of clear fluid which covers the lungs after having produced a partial collapse. The pleural surfaces are smooth and glistening. The lungs show an intense pulmonary edema, which has filled most of the alveoli with fluid. The entire dependent portion of the lungs—that is, the ventral half—may be completely filled with fluid so that the consistency is that of a solid jelly. On being sectioned the lungs exude a clear fluid that runs freely from the surfaces. The appearance of the cut surface varies from large areas where the air is completely replaced by fluid to other places where pink, air-containing areas are interspersed with red, fluid-containing portions. The bronchi and trachea are filled with fluid, or, in lesser degrees of pulmonary edema, they may contain a white froth. The bronchial and tracheal mucosa is pale, and the mediastinal lymph nodes are small.

Table I summarizes the observations made on 17 rats which were killed or which died at various intervals from 1 to 22 hours after poisoning. After the first hour, most of the lungs weighed more than the normal average (0.87 g. per 100 g. body weight). They showed considerable variation from rat to rat. Pleural effusion did not appear until the 2nd hour. From then on it increased somewhat irregularly until it reached a plateau after the 16th hour. A rat that died at 19½ hours showed the greatest amount of pleural effusion, 6.26 cc. per 100 g. body weight.

Microscopic Appearance of Lungs. The development of pulmonary edema can be easily traced, with individual variation, through the series of successively killed rats. The last 2 columns in Table I summarize the results. Perivascular edema appeared in both rats killed at the end of 1 hour after poisoning and alveolar edema appeared in 1 of the 2 rats killed at this time. The perivascular edema was more

marked in rats killed between 4 and 16 hours; the alveolar edema was most marked in rats which died or were killed 17 to 22 hours after poisoning. The final degree of this extraordinary edema is illustrated in Fig. 1, which is taken from a rat that died 17½ hours after the injection of ANTU. Here, the protein-containing edema fluid fills most

TABLE I
Observations on pulmonary edema and pleural effusion of wild Norway rats treated with ANTU

RAT NUMBER	SEX	KILLED OR DIED	TIME	LUNG WT. G./100 G. BODY WT.*	PLEURAL EFFUSION (CC.) PER 100 G. BODY WT.	ALVEOLAR EDEMA	PERIVASCULAR EDEMA
			<i>hrs.</i>				
1	F	K	1	0.74	0	0	±
2	M	K	1	1.62	0	++	+
3	M	K	2	1.13	0	+	±
4	F(pregnant)	K	2	1.34	0.10	±	++
5	F	K	4	1.17	0.42	++	+++
6	F	K	4	1.56	0.45	+	++
7	F	K	6	1.84	1.11	++	++
8	F(postpartum)	K	6	1.05	2.50	+	+++
9	F(pregnant)	K	10	0.56	2.92	++	++
10	F	K	10	1.40	3.36	++	+++
11	F(pregnant)	K	16	0.87	5.50	++	+++
12	M	K	16	1.00	0.30	+	±
13	F	D	17½	1.40	4.16	+++	+
14	M	K	18	1.17	1.80	++	+++
15	F	D	19½	1.19	6.26	+++	++
16	F	D	19½	1.84	3.80	+++	++
17	M	K	22	1.61	1.70	++	++

0 = none.

± = trace.

+ to +++ = degree of prominence.

* Average control value = 0.87 g. per 100 g. body weight.

of the alveoli in the ventral portion of the lung and even extends into the bronchi. Some of the alveolar ducts and a few of the alveoli are overdistended with air. Distention of the perivascular tissue is apparent. For contrast, a normal air-containing lung of a control rat is shown in Fig. 2.

The earliest change seen after poisoning is the distention of the perivascular lymphatics at the hilum of the lung with protein-con-

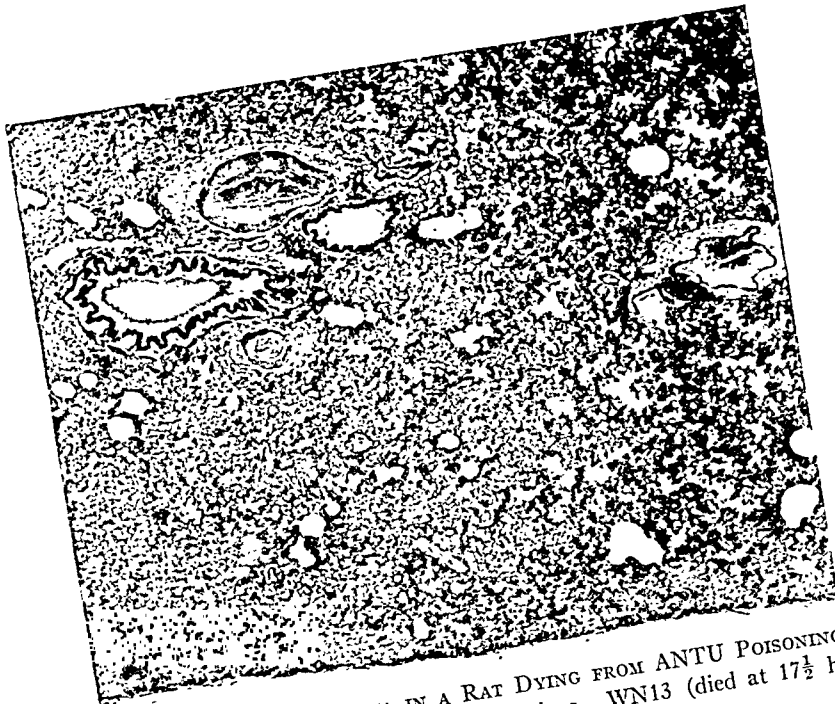


FIG. 1. PULMONARY EDEMA IN A RAT DYING FROM ANTU POISONING
 Note overdistention of air-containing portions. WN13 (died at $17\frac{1}{2}$ hours)
 X37.5

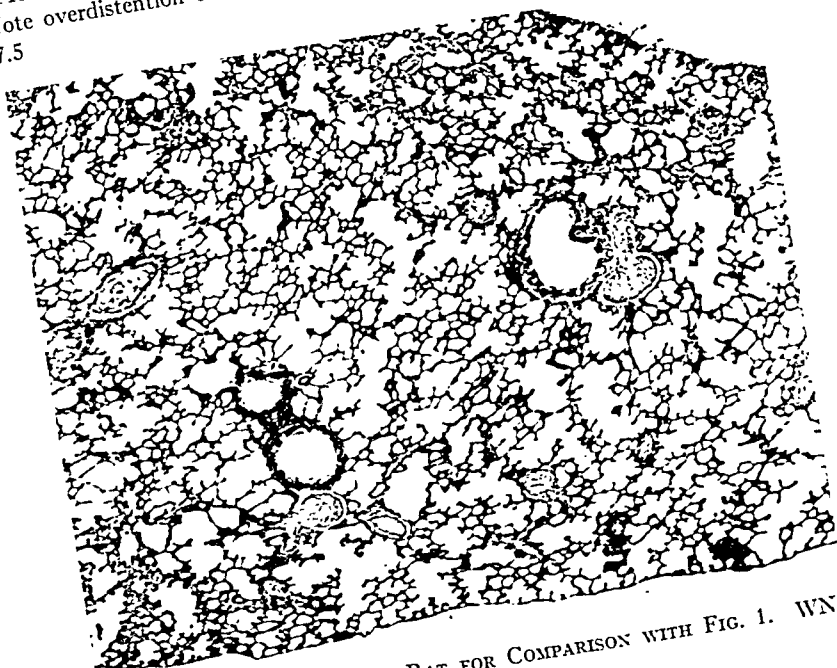


FIG. 2. LUNG FROM A CONTROL RAT FOR COMPARISON WITH FIG. 1. WN1009
 X37.5

taining fluid. Then, as the lymphatics and the perivascular tissues in both the hilum and periphery swell with fluid to a remarkable degree, fluid begins to appear in the alveoli, first lining and then filling them. Fig. 3, from a rat killed at 2 hours, shows the early distention of the

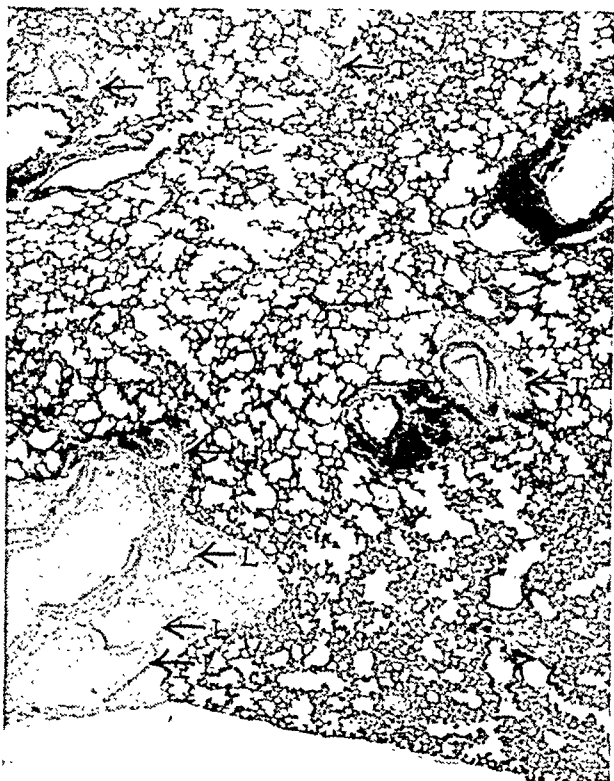


FIG. 3. DISTENDED PERIVASCULAR LYMPHATICS (L) AND TISSUES (T), WITH MOST ALVEOLI STILL AIR-CONTAINING. WN4 (KILLED AT 2 HOURS) $\times 25$

perivascular lymphatics and tissues. With higher magnification traces of fluid are just barely visible in some alveoli in this section.

The final extreme degree of distention of the perivascular lymphatics and tissues at the hilum is demonstrated in Fig. 4, from the lung of a rat killed at 22 hours. For comparison, the corresponding area at the hilum of a control lung is shown in Fig. 5. The large hilar vessel in the lower right-hand corner of Fig. 5 corresponds to the large vessel the



FIG. 4. MARKED DISTENTION OF PERIVASCULAR LYMPHATICS AND TISSUES AT THE HILUM OF THE LUNG

Arrows mark the lymphatics. WN17 (killed at 22 hours) $\times 70$

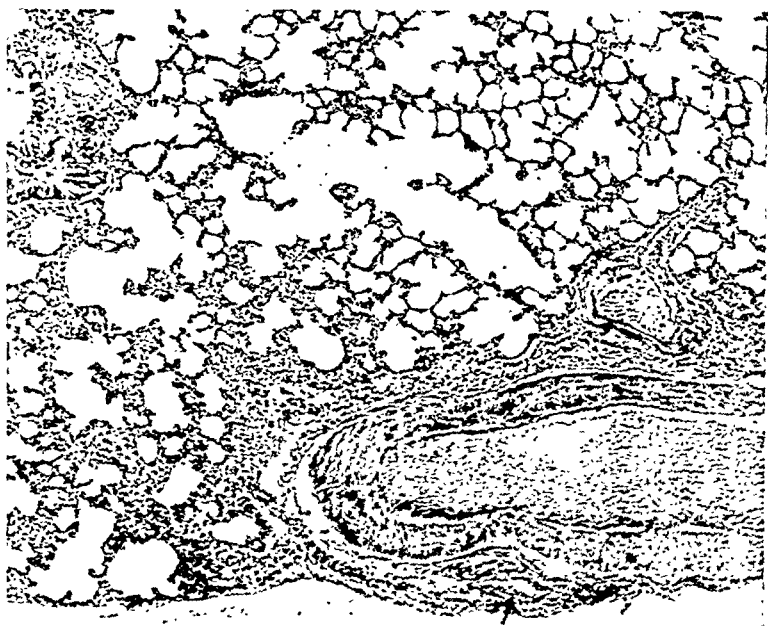


FIG. 5. A CORRESPONDING AREA AT THE HILUM OF A CONTROL LUNG FOR COMPARISON WITH FIG. 2. WN349 $\times 70$

edge of which is seen in the upper right-hand corner of Fig. 4. Fig. 6 shows at higher magnification the edema about a medium-sized artery and vein in the periphery of the lung of a rat killed at 18 hours.

When many of the alveoli become filled with fluid, the remaining air-containing alveoli become overdistended (Fig. 1). The overdistention of a few alveoli or alveolar ducts is maintained in spite of the compression of the lung as a whole which must result from the

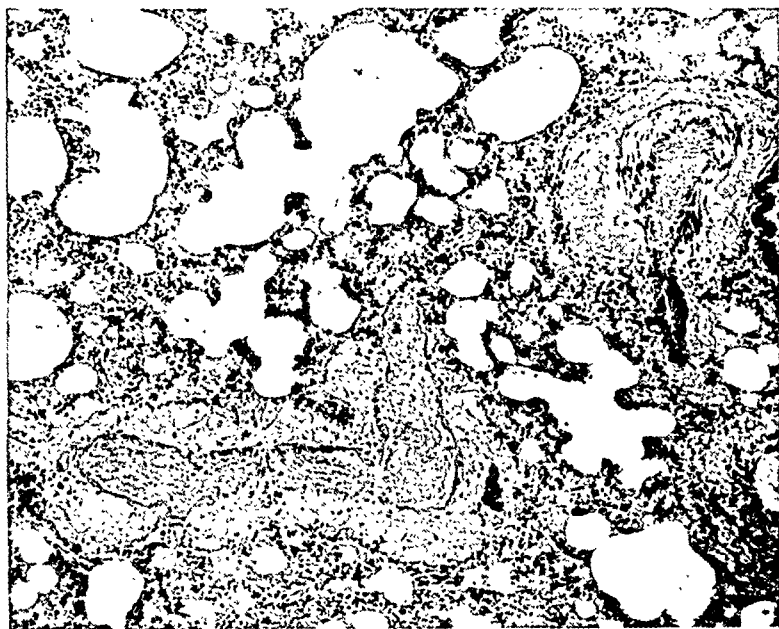


FIG. 6. EDEMA ABOUT MEDIUM-SIZED ARTERY AND VEIN IN PERIPHERY OF LUNG.
WN14 (KILLED AT 18 HOURS) $\times 100$

large pleural effusion developing along with the pulmonary edema. In many areas near the pleura in which a portion of the lung is partly filled with fluid and still partly air-containing, most, if not all, of the subpleural alveoli are filled with fluid. As might be expected, in the 3 long-living rats which died from the poisoning alone, the alveolar edema is more extensive than in the poisoned and killed animals.

The lungs of rats poisoned with ANTU do not show any definite vascular lesions, hyaline thrombi or hyaline membranes.

No correlation could be made between the state of pregnancy and the pulmonary changes. In neither of two fetal lungs were there any traces of pulmonary edema, nor did the fetal pleural cavities contain fluid. Although 3 males in this series had less pleural effusion than the corresponding females, this difference was not consistent in a few other animals. No conclusion therefore can be drawn as to sex differences.

Contents of Fluid in Lungs and Pleural Cavities. A protein-rich fluid can be seen in lymphatic channels, in the alveoli, and in the bronchi.

Many lymphocytes are found in the relatively normal lungs of control wild Norway rats, usually as localized accumulations next to a bronchus or a vessel. In the poisoned animals lymphocytes are scattered through the edematous perivascular tissues, and they are frequently seen in lymphatic channels.

In the poisoned animals a few polymorphonuclear leukocytes are seen in the alveolar fluid along with macrophages containing coal pigment. These polymorphonuclear cells are also found in the edematous perivascular tissues in varying numbers, occasionally being quite numerous. They can be found in the lymphatics much less frequently than the lymphocytes. In one of the 5 rat lungs stained for bacteria many gram-positive cocci were found. Only rare, scattered gram-positive cocci were found in the other lungs.

Erythrocytes have not been found in the edematous perivascular tissues or in the lymphatics. A few focal hemorrhages are seen in the lungs, not associated with any observed vascular or pulmonary lesion. They are interpreted as probable artifacts produced by killing or by autopsy trauma.

The pleural fluid contains protein in relatively high concentration (3.6 to 3.7 g./100 cc. in 4 wild Norway rats, whose final plasma protein concentration varied from 4.6 to 5.0 g./100 cc.). It contains enough fibrin to form a soft clot when removed from animals soon after death. The leukocytes in the pleural fluid of 5 rats varied from 360 to 1400/mm³. Most of the cells were mononuclear, but a rare polymorphonuclear leukocyte was seen. A few erythrocytes were seen also, but the possibility of contamination in removal could not be excluded.

Mediastinal Edema. To determine the relationship between the development of pulmonary edema and mediastinal edema, 10 domestic

Norway albino rats were used. Pleural effusion first appeared at 4 hours. Microscopic sections from the lungs and mediastinum of each rat show that the edema developed more rapidly in the lung than in the mediastinum. In a rat killed at 30 minutes, when only distended lymphatics could be found in the mediastinum, the lungs showed widespread distention of the perivascular lymphatics and tissues with fluid, and an early diffuse alveolar edema. In the 2 animals killed at 6 hours there were relatively large pleural effusions with moderate alveolar edema. The perivascular tissues were quite distended and the mediastinal tissues were edematous.

Incidental Disease. It must be emphasized that the 17 wild rats used in this study came directly from the streets and cellars with their naturally occurring diseases. Six of the rats had an acute or chronic pulmonary inflammatory disease, but this did not noticeably affect the development of the edema due to ANTU. The diseased areas were localized, and the edema in the rest of the lungs was quite similar to the edema in animals with no other pulmonary disease. Nine of the animals had a helminth infestation in the liver. One had an acute pyelonephritis. Only 5 had no incidental disease in a major organ. The 10 control rats were similarly diseased.

Other Organs. Changes in organs other than the lung, particularly in the liver, adrenals, spleen and lymph nodes are observed in wild rats, but their interpretation is obscured because of the incidental diseases and the variable conditions of the wild rats' life.

DOGS

Gross Appearance of Lungs. In the dogs, the pleural effusion and pulmonary edema were usually not as marked as in the rats, probably because the dogs received relatively larger doses and so died before the effects could become as marked as in the longer-surviving rats. In this larger animal, however, perivascular edema may be easily visible in the gross, forming rings as much as 5 mm. in thickness around the medium-sized vessels.

Microscopic Appearance of Lungs. The dog lungs show a pulmonary edema of moderate to marked degree which is quite similar to that found in rats. The concentration of protein in the fluid where it only partially fills an alveolus is much greater in the dog than in the

rat. In the dog it progresses to the extent of hyaline membrane formation. In those areas of the lung which are more markedly involved, the alveoli are filled with a fluid containing a few cells, in varying proportions—macrophages, lymphocytes, and polymorphonuclear leukocytes. The few cells seen in the bronchial fluid are mostly mononuclear. The perivascular lymphatics and tissues are tremendously distended with fluid. The lymphatics of the visceral pleura are distended and there are some localized areas in which the pleural tissues are greatly edematous. This is shown in Fig. 7, which is from a dog



FIG. 7. EDEMA OF THE VISCERAL PLEURA. DOG 17 (DIED AT 9 HOURS) $\times 75$

which died 9 hours after intraperitoneal injection. Another dog, killed $2\frac{1}{2}$ hours after receiving ANTU, showed an early edema.

Most of the dog lungs have a few foci of acute or chronic inflammation. There are a very few hemorrhages, either associated with a focal inflammatory lesion, or with probable trauma. Such hemorrhages varied in number and size and are considered incidental to the ANTU effects. Three dogs had a moderate number of polymorphonuclear leukocytes scattered through the alveoli. Only rare gram-positive cocci were found in the bacterial stains on the three lungs. No hyaline thrombi are found in the large or small vessels.

Lymph Flow Experiment. The right lymphatic duct of a dog was cannulated by Dr. Drinker in his usual manner. The conditions and precautions necessary in this difficult technical procedure are discussed in his monograph (6, pp. 11-14). Under these conditions, with reasonably constant cardiac activity, variations in lymph flow are produced by pulmonary changes. The dog was injected intravenously with 20 mg. of ANTU per kilogram of body weight. The results are described by Dr. Drinker in his monograph (6, pp. 39-43). Because of wartime security regulations he did not state that ANTU was the thiourea derivative used.

Within the first hour after the injection of ANTU a definite increase in lymph flow was found. The amount of lymph collected increased fairly rapidly for the first 7 hours and even more rapidly thereafter. A final value of 12.6 grams of lymph per 15-minute interval was attained at the end over 8 hours later, compared to 0.4 grams before the administration of ANTU. Anoxia and the terminal increase in respiratory activity are probable factors in the terminal acceleration, but even without this the increased rate of lymph flow is remarkable. Dr. Drinker gives a vivid description of the extreme pulmonary edema and the extraordinary distention of the perivascular tissues and lymphatic-draining trunks. He concludes that as the lymphatics become unable to remove the deluge of fluid coming from the capillaries, the excess floods out into the alveoli, producing death by asphyxia.

Hemodynamic Effects. In order to evaluate the role of possible cardiac changes in the production of the pulmonary edema, the hemodynamic changes in 2 unanesthetized dogs poisoned with ANTU were observed by Dr. Bing (7).

The observations were similar in both dogs, but they were more detailed in the case of one dog. This dog was placed on the operating table, where it remained during the half hour required for each set of readings. Between observations the dog was allowed to walk around the laboratory or lie down as it desired. No food or water was given the day of the experiment. Control readings were made on the preceding night.

The cardiac output was determined by direct Fick. A catheter was introduced into the right ventricle or auricle via the external jugular vein and its position checked by fluoroscopy. Samples of arterial blood

were taken from the femoral artery, while mixed venous blood was obtained through the catheter from the right ventricle. All blood samples were taken under oil and analyzed in the Van Slyke apparatus.

The oxygen consumption was measured by means of the closed circuit method. A Blalock mask (8) was used to connect the dog's

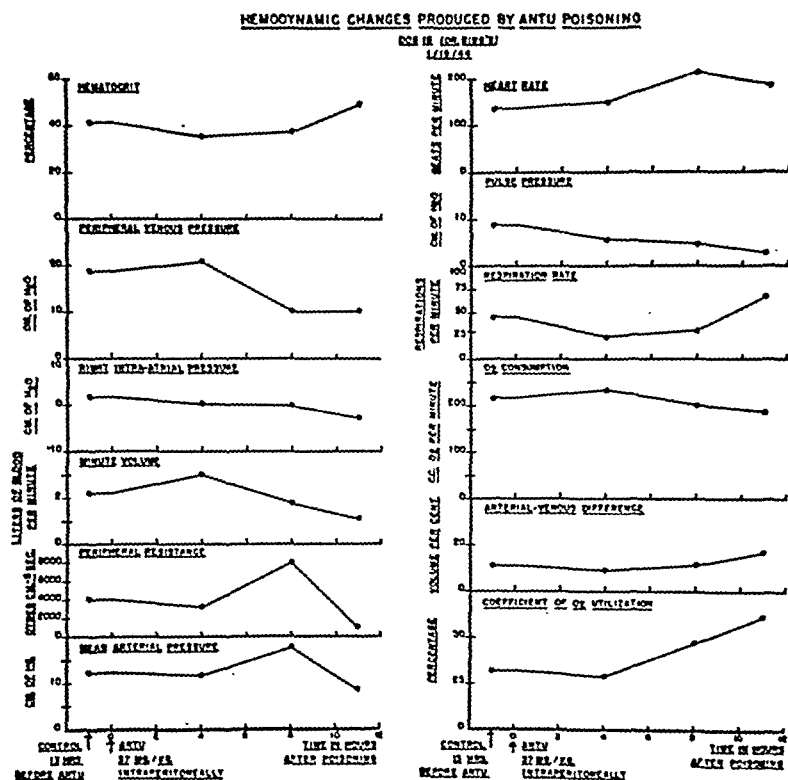


FIG. 8. HEMODYNAMIC CHANGES PRODUCED BY ANTU POISONING

head with the metabolism machine. Arterial blood pressures were optically recorded with the Hamilton manometer (9); right auricular pressures were obtained with a saline manometer. The peripheral resistance was calculated according to the formula of Apéria (10).

Observations were made before and after the injection of ANTU intraperitoneally (33 mg./kg.), and are represented graphically in

Fig. 8. Dr. Bing found a fall in peripheral venous pressure and a decrease in right intra-auricular pressure. According to him the decrease in these pressures was probably due to a decrease in circulating blood volume, as was indicated by a rise in the hematocrit (from 41.6 to 49.5), which was observed here as well as in other dogs and in rats. This animal received saline through the intracardiac catheter in order to prevent clotting in its lumen, and as a consequence the hematocrit did not rise as much as in animals which did not receive saline. It seemed possible that the decrease in venous return produced a fall in the minute volume of the heart, which at first was compensated by a rise in peripheral resistance. Towards the end of the experiment, however, the peripheral resistance and, with it, the mean arterial pressure declined. Other data are shown in Fig. 8. These cardiovascular changes seem to be due mostly, if not entirely, to fluid loss from the blood.

DISCUSSION

Pulmonary Edema. Although the evidence of pulmonary edema may develop early, being present and widespread in an hour in rats, the rats and dogs show little respiratory difficulty until 2 or 3 hours before they die, usually 12 to 24 hours later with the doses used. At death the pulmonary edema and compression by pleural fluid are extensive enough to indicate that anoxemia probably is a major factor in causing death.

From Dr. Drinker's experiment described above it seems evident that the pulmonary lymphatics become unable to drain the deluge of fluid which pours out of the alveolar capillaries and that the alveoli, bronchi, and pleural cavities fill with the excess fluid.

Dr. Bing's experimental results presented above are interpreted as indicating that the cardiovascular changes are secondary to the fluid loss in the lungs and pleural cavities. If the pulmonary edema had been caused by backward failure of the left ventricle, the right ventricular and eventually the right auricular pressures should have increased, owing to increased resistance to right ventricular output. No changes are seen microscopically in the myocardium. Furthermore, Drinker states (6, p. 44) that "increased pressure in the pulmonary capillaries does not readily cause recognizable pulmonary

edema unless coupled with heightened permeability, most frequently due to anoxia."

The edema fluid then is probably produced by an increased pulmonary capillary permeability. An interesting analogy is the striking localized edema of the head and neck of rabbits produced by paraphenylenediamine (11). Other factors and mechanisms involved in the production of pulmonary edema are discussed in a review by Henneman (12).

Pleural Effusion. Fluid is found in the pleural cavities after edema fluid appears in the lungs. This is shown in the series of 17 wild Norway rats and 10 domestic Norway rats described above.

The protein content of the pleural effusion produced by ANTU is about of the same magnitude as that of the organ lymph from dogs and other animals as listed by Drinker and Yoffey (Tables 18 and 20, 13), most of their values ranging from 2.8 to 5.3 mg. per cent. The few figures we have on rats (see above) indicate that the protein content of the pleural effusion produced by ANTU is somewhat less than that of the blood. Drinker (6) found in the dog mentioned above that the protein concentrations in the lung lymph, in the fluid from the trachea, and in the pleural fluid were identical. Another observation of his, of interest with regard to the permeability of the pulmonary capillaries, was that the lung lymph protein concentration remained almost the same before and during the entire experiment. The fibrinogen content of the pleural effusion is high enough to produce clotting, which occurs within a few minutes after the thoracic cavity is opened. In this it resembles pericardial and peritoneal fluid from normal healthy animals, which almost always clots (14). In summary, it would seem that the protein content of the pleural effusion is quantitatively similar to that of the lymph.

The figures above show that the cellular content of the effusion fluid is low, as is usual in noninfected serous fluids (15). In 2 rats (which died after 8 and 12 hours respectively) it was the same as the cell content of the bronchial fluid, within the limits of accuracy of the count (360 and 398 cells/mm³ and 560 and 580 cells/mm³ respectively). Polymorphonuclear cells were rarely seen among the lymphocytes and larger mononuclear cells. This corresponds with relatively normal lymph in which lymphocytes usually account for 95 per cent or more

of the cells present (13). Since some polymorphonuclear cells may be seen in the lungs of many of the animals, it may be wondered why they were not found in the effusion fluid of these two rats in larger numbers. The relatively early death of these rats may be the explanation.

CONCLUSIONS

Alpha-naphthyl thiourea produces a great increase in the permeability of the capillaries of the lungs of rats and dogs. The escaping fluid first fills the perivascular lymphatics and perivascular tissues and then later it fills the alveoli and a large part of the thoracic cavity. No other parts of the body show any edema. There is no ascites. The drug appears to have a selective effect on the capillaries in the lungs which produces a great flow of lymph from the lungs. This flow does not suffice, however, to prevent the filling of all the lung spaces and tissues. The fluid in the lungs and pleural cavities have similar protein and cellular contents, approximating the amounts present in blood serum. The capillaries show no actual damage and all of the effects are reversible. The pulmonary edema and pleural effusion, in addition to other factors, may result in death.

Acknowledgments. 1. This study was undertaken at the suggestion of Dr. C. P. Richter, who has supervised the experiments and encouraged the writer.

2. The author is indebted to Dr. A. R. Rich, who has been generous in consideration and careful in criticism of this paper.

3. Thanks are due to Dr. J. B. Frerichs, who examined much of the material before entering the Army.

REFERENCES

1. RICHTER, C. P., AND CLISBY, K. H.: Graying of Hair Produced by Ingestion of Phenylthiocarbamide. *Proc. Soc. Exp. Biol. and Med.*, **48**, 684, 1941.
2. RICHTER, C. P., AND CLISBY, K. H.: Toxic Effects of Bitter-Tasting Phenylthiocarbamide. *Arch. Path.*, **33**, 46, 1942.
3. RICHTER, C. P.: The Development and Use of Alpha-Naphthyl Thiourea (ANTU) as a Rat Poison. *J. Amer. med. Ass.*, **129**, 927, 1945.
4. DIEKE, S. H., AND RICHTER, C. P.: Age and Species Variation in the Acute Toxicity of Alpha-Naphthyl Thiourea. *Proc. Soc. Exp. Biol. and Med.*, **62**, 22, 1946.

5. ANDERSON, W. A., AND RICHTER, C. P.: Toxicity of Alpha-Naphthyl Thiourea for Chickens and Pigs. *Vet. Med.*, **41**, 302, 1946.
6. DRINKER, C. K.: *Pulmonary Edema and Inflammation*, Cambridge, Mass., Harvard University Press, 1945.
7. BING, R. Personal communication.
8. BLALOCK, A.: A Rubber Mask for Determination of Oxygen Consumption of the Dog. *J. Lab. and Clin. Med.*, **12**, 378, 1927.
9. HAMILTON, W. F., BREWER, G., AND BROTMAN, I.: Pressure Pulse Contours in Intact Animal; Analytical Description of New High-Frequency Hypodermic Manometer with Illustrative Curves of Simultaneous Arterial and Intercardiac Pressures. *Am. J. Physiol.*, **107**, 427, 1934.
10. APÉRIA, A.: Hemodynamical Studies. *Skandinav. Arch. f. Physiol.*, Supplement 16 (to Volume 83), 1940.
11. TAINTER, M. L., AND HANZLIK, P. J.: Mechanism of Edema Production by Paraphenylenediamine. *J. Pharmacol. and Exp. Therap.*, **24**, 179, 1924.
12. HENNEMAN, P. H.: Acute Pulmonary Edema with Special Reference to Experimental Studies. *New Eng. J. Med.*, **235**, 590, 1946, and **235**, 619, 1946.
13. DRINKER, C. K., AND YOFFEY, J. M.: *Lymphatics, Lymph, and Lymphoid Tissue*, Cambridge, Mass., Harvard University Press, 1941.
14. MAURER, F. W., WARREN, M. F., AND DRINKER, C. K.: Composition of Mammalian Pericardial and Peritoneal Fluids, Studies of Their Protein and Chloride Contents, and Passage of Foreign Substances from Blood Stream into These Fluids. *Am. J. Physiol.*, **129**, 635, 1940.
15. PADDOCK, F. K.: Diagnostic Significance of Serous Fluids in Disease. *New Eng. J. Med.*, **223**, 1010, 1940.

PENILE ULCER CAUSED BY MICROCOCCUS TETRAGENUS

BERNARD D. PINCK, M.D., AND BERTRAM ZHEUTLIN, M.D.

Since the discovery of *Micrococcus tetragenus* in 1881 by Koch and Gaffky, less than 200 cases of infection directly referable to this organism have been recorded. Although the paucity of reports in American literature suggests that such a disease occurs infrequently, Reimann believes that it is probably quite common, but is often disregarded or unrecognized in this country.

Micrococcus tetragenus, at first regarded as an innocuous saprophyte, was reported as a pathogenic organism in 1886 by Jakowski, and subsequent reports by Mya and Trambusti and Viquerat confirmed this finding. It is a gram-positive coccus frequently associated with other organisms in sputum, especially with the tubercle bacillus and Pfeiffer's bacillus. Smears from sputum or pus show large cocci arranged in pairs and fours, and surrounded by a broad capsule. In cultures the capsule is often absent. The colonies, which grow rather slowly, are white, are slightly smaller than those of staphylococci, and are quite viscid. The organism does not liquefy gelatin but it produces acid in glucose, lactose, saccharose, and mannite. Milk used as a culture medium becomes slightly acidified, and it usually is coagulated in from one to three days, but the coagulum is not digested.

The organism is ordinarily not virulent, and the infection follows a predisposing condition which reduces the resistance of the host and fosters the invasive quality of the organism. Sore throat, respiratory tract infection, anemia, abscesses, and urinary tract infection are reported to be the commonest predisposing factors. *Micrococcus tetragenus* infections have been observed also following typhoid fever, streptococcal septicemia, and brucelliasis. The infection ordinarily occurs in young adults.

The disease begins abruptly and the severity of its course is variable. There are chills, remittent fever, mild to moderate leukocytosis, and occasionally, splenomegaly. Approximately 25 fatal cases of septicemia have been recorded. The infection may become localized in various parts of the body, usually causing pneumonia, arthritis, empyema,

meningitis, and endocarditis. The occurrence of perinephric abscess has been recorded by Vease and of pyosalpinx by Wollgreen. Reimann reported prostatitis during septicemia and cultivated *Micrococcus tetragenus* from an urethral exudate. No previous description of genital ulcerative lesion has been discovered. A case of penile ulcer caused by *Micrococcus tetragenus* is reported here.

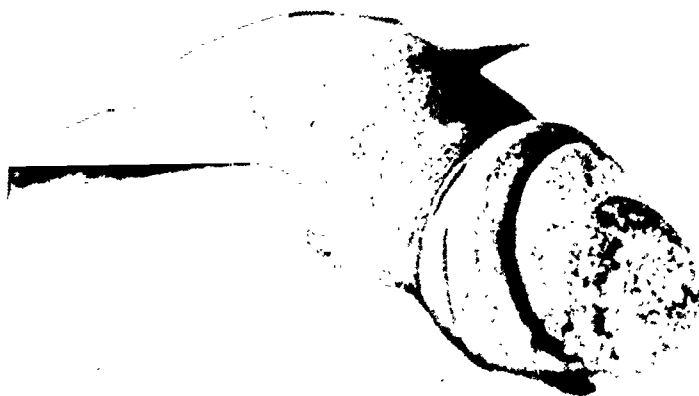


FIG. 1. PENILE ULCER CAUSED BY MICROCOCCUS TETRAGENUS

REPORT OF A CASE

The patient, a white professional soldier, aged 29, was admitted to the One Hundred and Twenty-First General Hospital on May 25, 1946 complaining of pain at the end of the penis of three days duration.

The family history was non-contributory.

The patient's past history revealed that the patient had had gonorrhea in 1943 treated with penicillin, without recurrence or reinfection. He denied syphilis by name, symptom, and treatment. There were never any complaints referable to the genitourinary system previous to the present illness, and the rest of the past history was non-contributory.

Three days prior to his admission to the hospital, the patient asserted that he fell onto the tailboard of a truck, striking his penis against a heavy chain. There was momentary pain which subsided in a few minutes. On the day of admission to the hospital the head of the penis began to swell and urination was difficult. The symptoms persisted and rapidly became more distressing; the initiation of

micturition was delayed, and obstruction seemed to be apparent at the meatus. With urination, possible only by straining, there seemed to be increasing swelling of the ventral section of the glans and frenum. On further questioning the patient admitted having practiced fellatio about twenty days before the onset of the lesion.

The physical examination revealed a well developed, well nourished white male who appeared moderately anxious about his condition. His skin, head, neck, abdomen, glandular, respiratory, and cardiovascular systems revealed no significant abnormalities. Main interest focused on the genitourinary system. There was swelling of the entire glans penis, most marked on the ventral side. At the end of the meatus was an encrusted ulceration which had no induration or discharge. There was no periurethral induration. The scrotal contents were normal. The prostate was normal in size, smooth, regular, and compressible.

Laboratory study at the time of admission showed that the red and white blood counts were within normal limits. The urine was clear, straw colored, and contained no albumin, sugar, red or white blood cells, or casts. The Kahn test was doubtful throughout the entire hospital stay with no significant change in titre, and repeated darkfield illuminations did not reveal the presence of *Treponema pallidum*. Culture and smears of the lesion were negative for gonococci, diphtheria bacilli and the only organism grown on culture taken from the surface of the lesion was *Staphylococcus albus*. The intravenous pyelogram and the urine culture revealed no significant abnormalities.

Continuous soaks of various sorts were used, but no improvement was noted. The lesion increased in size and depth until on the fourteenth hospital day, it extended halfway across the glans. The eschar, which was becoming thicker and harder, was now black and had rounded, well defined edges, and the meatal lips seemed almost occluded. On the fifteenth hospital day the patient was given 16 mg. of morphine and the crust was manually broken. The lesion then revealed greater depth than was at first suspected. The entire distal portion of the glans was gangrenous. There was a foul smelling, purulent discharge and the eschar clung to the devitalized shreds of the glans. Smears and cultures were immediately taken from the purulent exudate beneath the eschar. The smear showed encapsulated gram-positive cocci in pairs and tetrads. No other organisms were seen in the smears. The anaerobic cultures produced a pure growth of organisms identified as *Micrococcus tetragenus* by the standards set forth above. Aerobically a few colonies of *Staphylococcus albus* were noted.

The sixteenth day of hospitalization the gangrenous distal portion of the glans sloughed away completely, revealing the base of the lesion covered with a milky gray, foul smelling, purulent discharge. Smears and cultures again showed a growth of organisms identified as *Micrococcus tetragenus*. The histologic examination of the gangrenous portion of the glans revealed large collections of leukocytes with polymorphonuclear leukocytes predominating, while the main portion of the microscopic section consisted of granulation tissue at various stages of organization. Under oil the section showed numerous organisms morphologically resembling *Micrococcus tetragenus*.

An indwelling catheter was inserted and therapy with zinc peroxide was begun.

Two days after the first application of zinc peroxide the lesion was washed with azochloramide and smears and cultures were taken from the base of the lesion. The cultures still showed a pure growth of *Micrococcus tetragenus*. Two more applications of zinc peroxide were made, each one being washed off with azochloramide after forty-eight hours. After the third and last application of zinc peroxide was removed with axochloramide, the lesion showed remarkable improvement. It had a pink base with speckled areas of gray exudate. Smears and cultures became negative after the third application of zinc peroxide. Treatment with sulfadiazine and intramuscular injection of penicillin was then begun and the indwelling catheter was retained. On the twenty-fourth hospital day, the lesion showed a clear red base with the first evidence of epithelialization from the edges.

The lesion improved uneventfully from then on, and on the thirty-sixth hospital day, after considerable epithelium had formed, the catheter was removed. Seven days later the lesion had completely healed without constriction of the meatus and the patient was discharged from the hospital. About one tenth of the glans was lost, but a three month follow up of the patient disclosed that there had been complete recovery of normal urinary and sexual function.

SUMMARY

Micrococcus tetragenus infections are probably of more common occurrence than is generally recognized. The organism is of low virulence and infection follows ordinarily a predisposing disease which reduces the resistance of the host. A case of gangrenous penile ulcer caused by *Micrococcus tetragenus* is reported.

BIBLIOGRAPHY

1. REIMANN H. A.: *Micrococcus Tetragenus* Infection. J. Clin. Investigation, 14: 311-319 (May) 1935.
2. JAKOWSKI, M.: Grzybki chorobotwórcze [Pathogenic micrococci]. Gaz. lek., Warsaw, s.2, 6: 166, 1886.
3. MYA AND TRAMBUSTI: Cited by REIMANN.
4. VUQUERAT: Der *Micrococcus tetragenus* als Eiterungserreger beim Menschen. Ztschr. f. Hyg. u. Infektionskr., 18: 411, 1894.
5. BIRKS, A. H., THORNLEY, R. T., AND FAWCUS, R. A.: Septicaemia due to *Micrococcus tetragenus* as a Cause of Pyrexia at the Front. Quart. J. Med., 10: 1-6, 1917.
6. GAYET: Septicémie à tétragène pur chez un urinaire. J. d'urolog., 24: 72-74 (July) 1927.
7. MÜLLER, R.: Ueber abdominelle Infektionen mit *micrococcus tetragenus*. Wien. Klin. Wchnschr., 17: S15-S19, 1904.
8. KIMMERLE, A.: Zwei Fälle von Tetragenusinfektion. Fortschr. d. Med., 48: 305 (April 18) 1930.
9. VEASE: Cited by REIMANN.

PROCEEDINGS OF THE MEETINGS OF THE JOHNS HOPKINS MEDICAL SOCIETY

HELD IN HURD MEMORIAL HALL, NOVEMBER 11, 1946

The Strain Isolation and Serologic Studies of Influenza in Baltimore.

DR. THOMAS G. WARD (Department of Medicine).

Dr. Ward's report will be published in a forthcoming issue of the Bulletin.

DISCUSSION

Dr. A. M. Fisher: It would be interesting to know how long immunity lasts in patients who have had influenza and have developed protective antibodies against the disease. I have heard that it does not last as long after a natural infection as after vaccination. I wonder if that has been confirmed or if any of the patients have been tested after six months or a year for protective antibodies.

Dr. Ward: So far as I am aware there are no adequate studies to cover Dr. Fisher's question. Dr. Francis, at Michigan, feels that individuals who have been vaccinated as long as a year are still more immune than unvaccinated persons, or at least the former group has a lower attack rate for influenza.

Hemagglutination inhibition antibodies against both influenza "A" and "B" are present in practically all adult sera, some in fairly high titer, 512 to 1024 final dilution of the sera. These seem to have no effect on prevention of the disease in man, as sera collected in the early days of disease in cases of influenza will show these antibodies.

These antibodies may be natural in occurrence or may be the result of previous exposure to "A" and "B" influenza virus.

The point is excellent and we hope to make certain observations along this line during the next epidemic.

The Etiological Problem Presented by Calcified Chest Lesions in the Presence of Negative Tuberculin Reactions. DR. JANET HARDY (Department of Pediatrics).

Evidence has been accumulating to suggest strongly that calcified lesions seen on roentgenograms of individuals reacting negatively to relatively large doses of tuberculin may be of non-tuberculous etiology. The frequency of such calcified lesions has been demonstrated to have a very definite geographical distribution with an area of high prevalence in the Mississippi basin and the eastern slope of the Appalachian plateau.

Studies done by Christie and Peterson in Tennessee, and by Palmer on student nurses all over the United States, show a strong correlation between sensitivity to histoplasmin and calcified pulmonary lesions, suggesting that infection with histoplasma or some antigenically related organism is the etiological agent. Sayers and Merriwether suggested that *Aspergillus niger* is the infecting organism responsible for miliary pulmonary lesions healing with calcification. Aronson and Cox have both shown the relationship between infection with coccidioidomycosis and calcified lung lesions.

In the present study,¹ a group of 312 patients now between 15 and 30 years of age, and followed an average of 12.6 years since a primary tuberculous infection, has been retested intradermally with tuberculin and examined by roentgenograms of the chest in an effort to determine whether tuberculosis may be an etiological agent in the calcified chest lesions of negative reactors to tuberculin. It was found that of the 59 individuals having severe childhood infections, all are still hypersensitive to tuberculin a minimum of ten years after their tuberculous infection was first recognized. Of the 171 patients having mediastinal tuberculosis during childhood, only 2% fail to react to 1 milligram of tuberculin, and of the 82 patients who had a positive reaction to tuberculin but no x-ray evidence of pulmonary involvement 6% are now insensitive to 1.0 milligram of tuberculin. The rate of positive tuberculin tests in the community is not definitely known, but in a high school in a most congested area among the colored race it is only about 40%, and among the student nurses in their preclinical training, it is only about 15%. From these data it is concluded that hypersensitivity is in general retained following a primary tuberculous infection and that some other etiological agent is responsible for the high incidence of calcified chest lesions seen in tuberculin-negative individuals in the areas of high prevalence of this finding.

The Physiology of the Prostate Gland. DR. WILLIAM W. SCOTT (Department of Urology).

As an introduction to the subject, the principal methods of investigating prostatic function were enumerated, stressing particularly the information gained by a study of prostatic secretion in the dog. Illustrations were presented to show the dependence of the prostate and its secretion on androgens, castration abolishing prostatic secretion and injected androgens restoring it. Identical effects of those produced by castration were shown to be induced when estrogens were injected. Starvation effects on prostatic secretion were shown to be due to pituitary failure. A review of the known chemical constituents of the prostate gland and its secretion was presented including the important enzymes, acid phosphatase and fibrinolysin. The *in vitro* action of human prostatic slices on estrogens was discussed briefly. From these studies it was concluded that normal prostatic slices do not cause a *net* decrease or increase of the estrogenic activity of added estrogen, nor do estrogens have any effect on the rate of respiration of the slices.

DISCUSSION

Dr. J. A. C. Colston: Dr. Scott's presentation has certainly been most comprehensive and I think everyone will agree that it has brought us up to date in regard to our present knowledge of the physiology of the prostate gland. The problems which present themselves are numerous and pertain not only to the field of physiology but to chemistry and pathology and particularly to endocrinology. I am very much afraid, however, that you all would agree with me with my background—or perhaps, let us say, my lack of background—of experimental laboratory work that it would be hazardous if I should try to enter into any detailed discussion of these problems or their solution. I only hope that the rest of the members here have the satisfaction that I and the other members of the Brady staff have in the knowledge that our laboratories are reopening and I have every hope that

¹ Hardy, J. B., Persistence of Hypersensitivity to Old Tuberculins following Primary Tuberculosis in Childhood. *Amer. J. of Pub. Health*, 36, 1417 (Dec. 12, 1946).

with the work that has been undertaken, some definite light will be thrown on some of these blind spots that Dr. Scott has indicated.

Dr. J. E. Howard: Dr. Scott's interesting graph showing what happens to the starving dog brings up this possibility. Supposing you found a fat fellow with a little carcinoma of the prostate, you might figure on castration at least for a few months by giving him the starvation treatment. A second thought is that you might effect that gonadal atrophy equally well by x-ray of the pituitary, because the end result would probably be the same as with castration. Lastly, what light do the physiological studies throw on a possible hormonal cause for the prostatic hypertrophy which comes on with advancing years.

Dr. Scott: In answer to Dr. Howard, may I say that it would be of great interest to see the effect of a period of starvation on prostatic cancer in a fat man. To my knowledge, pituitary irradiation has not been carried out in cases of metastatic prostatic cancer. Theoretically it should work, if androgen is responsible for the growth of tumor. I am not sure that it is. Castration may remove carcinogen; estrogen may neutralize a carcinogen. This carcinogen may not be an androgen.

With regard to benign prostatic hypertrophy, there is an effect of castration or estrogen administration on these glands. However, it is impossible in the majority of instances to wait the period of 90, 120 or 150 days to observe an effect. When a man presents himself with benign prostatic hypertrophy with acute retention of urine, it is an emergency and must be treated as such by appropriate surgical procedures. I do believe that further studies along the lines presented this evening will clarify the situation and I do believe, though I hesitate to say at this time, that some day benign prostatic hypertrophy will be a medical problem.

Dr. M. M. Ravitch: Dr. Scott, is the prostate the source of the fibrinolysin which produces the liquefaction in the blood after sudden death? If so, is this due to an agonal secretion of prostatic fluid? Would prostatectomy inhibit this activity in people or possibly animals?

Dr. Scott: Dr. Ravitch, I am unable to answer your question. It does seem clear that the source of the fibrinolysin is the prostate and not the seminal vesicles.

Dr. Evelyn Howard: I think the antagonism between estrogen and androgen is interesting and significant. There has been some difficulty in detecting such antagonism, for example in the earlier work on embryonic differentiation of the reproductive tract, but studies are beginning to make sense in this direction. I would like to ask how this fits in with the effects of estrogens on prostatic hypertrophy. Could you go into that?

Dr. Scott: Personally, I think that benign prostatic hypertrophy is a tumor and not an overgrowth of the normal prostate; but there is evidence that benign prostatic hypertrophy is an overgrowth and is sensitive to androgen withdrawal. Androgen withdrawal can be accomplished by castration or its effect nullified by estrogen administration.

Guest: I would like to know if anything is known about the mechanism by which androgen and estrogen inhibit one another.

Dr. Scott: I know of no answer to that. I would like to know the answer myself and think perhaps through the study of prostatic tissue slices and slices of other secondary sex glands that we may in time learn the answer to this question; these are simply results of the experiments described, and tell us nothing of the mechanism. It is difficult for me to see from the basis of these experiments just what the mechanism is. I can not explain it through the pituitary. I think perhaps it is a direct effect but what that mechanism is I cannot say.

Dr. J. E. Howard: Well, Dr. Scott, if it is a direct effect, certain cells reflect that direct

opposition in a considerably different manner, because the ratio of antagonism as related to vaginal epithelium is quite different, in our opinion at least, from what you showed in the relative ratios in your prostatic tissues in which I know there is no direct effect. What was your ratio?

Dr. Scott: About 20 to 1.

Dr. J. E. Howard: Certainly there is no antagonistic effect of estrogen on nitrogen or potassium retention.

Dr. Scott: We do not know what the castration effect is on nitrogen retention in the patient with prostatic cancer.

BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers
and not necessarily those of the members of the
Editorial Board of this Journal)

The Anatomy of the Bronchial Tree. By R. C. BROCK. Illus. 96 pp. \$12.00
Oxford University Press, New York, New York, 1946.

Advances in anatomy were originally largely the work of surgeons, yielded for a time to the professional anatomists, and are once more chiefly the result of the work of surgeons.

The present work, by a well-known English thoracic surgeon, is infinitely more complete—and perhaps more accurate than the treatment of the subject in any anatomy text. It is certainly more lucid and readable than some anatomical studies on the same subject by anatomists presented for surgeons. The system of bronchial nomenclature is both reasonable and simple. The book is well illustrated with x-rays, bronchograms, photographs of metal bronchial casts, colored plates of the projections of the bronchial segments, photographs of dissection, etc.

Perhaps the chief fault is that the work is done entirely from the viewpoint of the surgeon attempting to localize a lung abscess, and too little from the standpoint of the surgeon planning pulmonary resection, for whatever cause.

Nevertheless, this is an invaluable source book for those interested in the localization of pulmonary disease.

M. M. R.

The Centennial of Surgical Anaesthesia. Compiled by JOHN F. FULTON and MADELINE E. STANTON. 102 pp. \$4.00. Henry Schuman, New York, New York, 1946.

In this year of the centennial of surgical anesthesia, the Yale historical library has published an annotated catalogue of surgical anesthesia compiled by John F. Fulton and Madeline E. Stanton. To those interested in the early history of anesthesia this bibliography will be most welcome. The short biographic sketches together with the annotations enhance the value of this brochure not a little, and possibly will extend its appeal beyond the domain of the bibliophile.

M. H. H.

The Challenge of Polio. By ROLAND H. BERG. 208 pp. \$2.50. The Dial Press, New York, New York, 1946.

This small book was written primarily to inform the many people who have given dimes to the National Foundation for Infantile Paralysis, of what was being done with their money. It makes no pretense of being other than a popular account, pitched at about the level of the newspapers and digest magazines. The style,

which is the current rather breathless journalistic variety, and the continuous effort to dramatize the subject will doubtless not bother most readers but may discourage those with serious scientific interests. It is an ambitious task to critically evaluate the large amount of material represented by the research done with National Foundation support but Mr. Berg tells a story which, for the most part, is adequate. Unfortunately, the book does not seem to have any well defined plan; chapters skip from portals of entry of virus to vaccination and back to portals again. The last chapter, however, which is the best, summarizes the subject quite adequately.

There are, as might be expected, numerous inaccuracies, many of which could have been corrected by consultation with the persons whose work is quoted. For example, at one point the failure to distinguish monkeys from chimpanzees implies an inability to appreciate the large role which host differences have played in experimental work with this disease. In two other places the totally erroneous picture of monkeys "hauling themselves painfully about their cages whimpering like sick children" will doubtless give comfort to the antivivisectionists who are constantly looking for cause to attack medicine. (For the record—paralysed monkeys give no evidence of being in pain and certainly do not whimper.) But things of this sort will not prevent the non-technical readers of the book from gaining much useful information from it.

H. A. H.

Clinical Hematology. By MAXWELL M. WINTROBE. 2 Ed. Illus. 862 pp. \$11.00
Lea and Febiger, Philadelphia, Pennsylvania, 1946.

The second edition of this excellent monograph on Hematology has been greatly modified and enlarged with the addition of many new illustrations. Recent advances in the field have been covered including the structure and use of folic acid, new data on the Rh factor and its relation to hemolytic transfusion reactions, and the effect of the nitrogen mustards on cellular mechanisms. A very worthwhile chapter on the metabolism of the erythrocyte has been added.

The author has done an excellent job of assembling the enormous amount of material in this field in a comprehensive manner while at the same time maintaining a thoroughly practical viewpoint. As a result this volume is valuable to the specialist as well as to the student and the average practitioner. Especially helpful are the cross references by page number in each chapter to related material in other sections of the book.

A. M. H.

Development Anatomy. A Textbook and Laboratory Manual of Embryology. By LESLIE BRAINERD AREY. 5th Ed. Illus. 616 pp. \$7.00. *W. B. Saunders, Philadelphia, Pennsylvania, 1946.*

It would be difficult to find a more systematic, comprehensive, and lucid account of general vertebrate embryology than that offered by Arey in this latest edition of his widely known textbook. As before, the book is divided into three main sec-

tions: (1) general development, (2) special development (organogenesis), and (3) a laboratory manual for the study of chick and pig embryos. Emphasis throughout Parts I and II is placed on human embryology and strengthened by comparisons with other vertebrate groups.

Subjects treated in Part I include the origin, discharge, and union of sex cells, cleavage and gastrulation, fetal membranes of vertebrates, human embryos and their membranes, and human placentation. The new stress on human development has been made possible by the discovery and study in recent years of very early human embryos. In addition to altering the organization and content of these topics, the author now presents two entirely new and, on the whole, well-considered chapters summarizing the hormonal control of reproductive cycles and the fundamental concepts and problems of experimental embryology. The previously lengthy chapter on teratology has been drastically reduced to a few pages which, along with a short section on twinning and duplication, are now included under experimental embryology. Also discussed in this same chapter are the interpretations of early stages, the concepts of potency, embryonic induction, and gradients, and the role of genetic, hormonal, and nervous influences in vertebrate development.

Changes in Parts II and III are restricted largely to corrections and additions made necessary by discoveries during the last six years. The organogenesis of each system of the body is discussed separately and in detail. At the end of each section appears a brief comment on the anomalies which arise as a result of faulty development.

Like the preceding edition, this book is handsomely printed and well written. Its information is authoritative and its format admirably suited to both straight reading and reference work. Individual topics are easily located because the subject matter is divided into logical units, the names of structures are italicized, and the book is very well indexed. A total of 588 excellent text figures, several of them in color, make structural relationships more clear. For readers interested in pursuing certain subjects further or in following up the new and controversial interpretations discussed in the text, there is at the end of each chapter a list of references which, for the most part, cover the essential literature very adequately. All features combine to make a book which would be a valuable asset to any medical library.

F. E. W.

Disorders of the Blood. By LIONEL E. H. WHITBY and C. J. C. BRITTON. 5th Ed. Illus. 665 pp. \$10.00. *The Blakiston Company, Philadelphia, Pennsylvania*, 1946.

Although there are several outstanding and exhaustive general works in hematology this is an excellent and worthy addition to them. It is clearly and concisely written.

In general the opinions offered are the most commonly accepted ones. However, the authors do not discuss in any detail and frequently do not mention contradictory

observations to certain statements they make. This is illustrated by the opinion that there is no real difference in the fragility of reticulocytes and more mature erythrocytes. Actually, there is much disagreement on this point. The statement that paroxysmal (cold) hemoglobinuria is due to a peculiar cold agglutinin is of interest for the *in vitro* hemolysis of this system will occur without agglutination. Furthermore, the cold agglutinin and hemolysin are apparently separate antibodies. The implication that marmite is effective in macrocytic anemias because of the extrinsic factor it contains is debatable in light of the present knowledge of "folic acid."

The only striking omissions are those of discussion of the more recent observations relative to the pathogenesis and therapy of pernicious anemia; the concepts of "hypersplenism"; anti-hemophilic fractions of plasma; and much work on iron metabolism.

The chapter on routine techniques is excellent.

The bibliographies are relatively short but quite adequate for further casual study.

Of great assistance to the reader is the careful cross index by page numbers found scattered through the text at pertinent points. This simplifies quick reference and eliminates repetition.

P. F. W.

Edinburgh Post-Graduate Lectures in Medicine. Vol. III. Published for the Honyman Gillespie Trust. 587 pp. \$15.00. *Oliver and Boyd, Tweeddale Court, Edinburgh, 1946.*

In this third volume of the "Edinburgh Post-Graduate Lectures in Medicine", thirty-three lectures given under the Honyman Gillespie Trust are included. This lectureship in Scotland is somewhat comparable to the Harvey lectures in the United States. The lecturers in this group, at least, are almost entirely from Scotland, although some are from England. If there is any defect to the book at all, it is that because of the exigencies of war, it was published in 1946 despite the fact that the lectures were given in 1942 and 1943. Despite the disadvantage of this lag period, the lectures are quite up-to-date; thus, in Professor Mackie's talk on "The Problem of Air-Borne Infection", the discourse includes everything except Robertson's most recent work.

Among some of the outstanding chapters are "The Differential Diagnosis of the Chronic Affections of the Lungs", by Charles Cameron. Learmonth's essay on "Reflex Vasodilatation in Surgery", is also of interest. Other excellent chapters are those by Agnes R. MacGregor, K. Paterson Brown, A. J. C. Hamilton, and Douglas Miller. McWhirter's chapter on "The Value of Post-Operative Radiotherapy in Carcinoma of the Breast", considers the extensive experience of the Royal Infirmary in Edinburgh with 1,879 carcinomas of the breast seen in a twelve year period. The case for post-operative radiation is well supported by McWhirter's figures. In the chapter by Clayson on "Modern Trends in Preventive and Social Aspects of Tuberculosis", the interesting confession is made that just before

the war, of 1,300,000 cattle in Scotland, 650,000 were infected with the tubercle bacillus and that the control is so slow that only 6.5 per cent of the cattle have been tested as free from infection.

The lectures in this book are of the high scholastic as well as medical caliber that one would expect to come from Edinburgh. For those of us who have studied in that medical center, as well as all other medical readers, this book should have an appeal.

H. N. H.

Gynecological and Obstetrical Pathology. By EMIL NOVAK. 2nd Ed. Illus. 570 pp. \$7.50. W. B. Saunders Company, Philadelphia, Pennsylvania, 1947.

The second edition of "Gynecological and Obstetrical Pathology", W. B. Saunders Co., by Emil Novak has finally made its appearance. I say "finally" because the demand for the book while out of print for the past two years has been enormous. There are several reasons for this: the excellence of the first edition; the great demand from discharged medical officers who are seeking training in gynecology; the requirement of the Obstetrical and Gynecological Specialty Board of a knowledge of pathology; and finally, the fact that the book is unique. There is no other book in the English language that covers the subject of gynecological pathology so concisely and yet so completely. The book is written from the author's own extensive experience in this branch of pathology, without attempting to give all the conflicting views on controversial subjects. This makes the book readable and clear, even to the relatively untrained. However a small bibliography is appended to each chapter for the convenience of those readers who are interested in a more comprehensive understanding of the subject.

The first chapter deals with the endocrinology of the menstrual cycle and pregnancy in a simple, concise way. In the next 28 chapters the gross and microscopic pathology of neoplastic and inflammatory diseases of the female generative tract is considered. Correlation between the pathological and clinical aspects of gynecology is in evidence throughout these chapters and, in the opinion of the reviewer, this is one of the most valuable aspects of the work. Chapters 30, 31, 32 and 33 deal with special subjects, namely ectopic pregnancy, pelvic endometriosis, implantation and placentation, and hydatidiform mole and chorioepithelioma malignum. The final chapter by L. M. Hellman deals with abnormalities and diseases of the placenta and appendages (other than hydatidiform mole and chorioepithelioma).

The new edition has expanded from 496 to 570 pages. Most of this is due to an increased number of illustrations. The first edition contained 427 pictures, whereas the second edition has 542. There was but one colored plate in the first edition and the present one contains 15. The only criticism which could be offered might be directed at the illustrations. Better sections might have been selected for the illustration of some typical lesions and more attention might have been paid to the reduction of the illustrations to the optimum size. The character of the illustrations is not quite up to that of the first edition because of the use of poorer quality paper. This is probably unavoidable due to the post-war shortage of paper.

On the whole the essential facts of obstetrical and gynecological pathology are well told and the second edition should continue to be the standard work in this field.

R. W. TEL.

Heparin in the Treatment of Thrombosis. By J. ERIK JORPES. 2nd Ed. Illus. 260 pp. \$6.50. Oxford University Press, New York, New York, 1947.

This book by Jorpes is the second edition of his monograph first published in 1939. It is indeed a classic. The development of heparin is due primarily to three groups of men. First, Howell and McLean of Baltimore; second, Jorpes and his collaborators of the Caroline Institute in Stockholm; and third, Charles and Scott and their co-workers in Toronto. The initial work done by Jay McLean in discovering heparin as a sophomore medical student at Johns Hopkins University in 1916, should make this subject one of especial interest to all Baltimoreans.

The new edition is much more complete than the previous one. The clinical data concerning the effect of heparin is brought up-to-date, and the American Literature is given consideration as much as is the Swedish. Considering the fact that Dr. Jorpes is primarily a chemist, the clinical aspects of this book are very well presented. His discussion, for example, of the pathology of deep vein thrombosis leaves little to be desired. The illustrations in the book are excellent, and the presentation of the subject is thorough and adequate in every way. It is a book to be recommended.

H. N. H.

Journal of the History of Medicine and Allied Sciences. Vol. I. 182 pp. \$2.50. Henry Schuman, New York, New York, 1946

With the present number, a new journal of medical history makes its debut. As the editor, Dr. George Rosen, says in the preface, its purpose is "to provide another focus for studies in medical history" (p. 4), "to cultivate medical history . . . as a vital, integral part of medicine" (ibid.), and "to present studies that can be of interest to as large a section of the medical profession as possible" (p. 5). While promising to be very broad in its scope and to maintain "the highest literary and scholarly standards" (ibid.), it will yet consider bibliographies and philological studies as more properly belonging to the *Bulletin of the History of Medicine*.

The broad scope of the journal is evidenced by the articles contained in this number. There are two contributions to *Primitive medicine* by E. H. Ackerknecht ("Incubator and Taboo") and L. C. MacKinney ("Animal Substances in *Materia Medica*"). *Anatomy* is dealt with by Charles Singer ("Some Galenic and Animal Sources of Vesalius") and J. B. de C. M. Saunders and C. D. O'Malley ("Bernardino Montaña de Monseratte"). Jane M. Oppenheimer ("A Note on William Blake and John Hunter") and Phyllis Allen ("Medical Education in 17th Century England") discuss chapters in the history of *English medicine*, while the articles by J. C. Trent ("The London Years of Benjamin Waterhouse") and P. I. Nixon ("Dr. Benjamin Harrison, Temporary Texan") can be assigned to the domain of *American*

medicine. The allied sciences of *pharmacy* and *dentistry* are represented by George Urdang ("Pharmacopoeias as Witnesses of World History") and Curt Proskauer ("The Two Earliest Dentistry Woodcuts"). Besides the articles, which fill the bulk of the issue, there is also a section for "Notes and Queries," edited by Max H. Fisch, and another section for "Book Reviews."

Altogether it can be said that in this first issue the Journal introduces itself as a medium for scholarly papers and in a form which is attractive by reason of its clear print, abundant illustrations and convenient format. This, together with the many well-known names constituting the Board of Editors and Consulting Editors, will assure it wide attention in this country as well as abroad.

O. T.

The Marihuana Problem. By the Mayor's Committee on Marihuana. 200 pp. \$2.50. Jacques Cattell Press, Lancaster, Pennsylvania, 1945.

The Mayor's Committee to study the marihuana problem consisted of two internists, three psychiatrists, two pharmacologists and one public health expert, appointed by the New York Academy of Medicine. It included such well-known names as McKeen Cattell, Robert F. Loeb, Karl M. Bowman, David Wechsler and S. Bernard Wortis. They concluded that the marihuana user does not come from the hardened criminal class, and there was found no direct relationship between the commission of crimes of violence and marihuana. Smoking marihuana can be stopped abruptly with no resulting mental or physical distress comparable to that of morphine withdrawal in morphine addicts.

The clinical studies were made upon prisoners who volunteered for the study. Although some of the subjects became restless and talkative under the marihuana influence, a mental state characterized by a sense of well-being, relaxation and unawareness of surroundings, following by drowsiness, was present in most instances when the subject was left undisturbed. In company the subjects were lively and given to talkativeness, fits of laughter and good-natured joking. In a limited number of the subjects there were alterations in behavior giving rise to anti-social expression. In the total group of 77 persons studied, what are known as psychotic episodes occurred in 9 of the subjects. In the clinical study of the effect of marihuana on functions of the various organs of the body, there were found an increase in pulse rate and blood pressure and an increase in blood sugar and metabolic rate. Static equilibrium and hand steadiness were the functions most strongly affected by marihuana. In an effective dose the drug impairs intellectual functioning in general.

Mayor LaGuardia summarized his attitude as follows: "I am glad that the sociological, psychological and medical ills commonly attributed to marihuana have been found to be exaggerated insofar as the City of New York is concerned. I hasten to point out, however, that the findings are to be interpreted only as a reassuring report of progress and not as encouragement to indulgence, for I shall continue to enforce the laws prohibiting the use of marihuana until and if complete

findings may justify an amendment to existing laws. The scientific part of the research will be continued in the hope that the drug may prove to possess therapeutic value for the control of drug addiction."

This study has been subjected to severe criticism by the Journal of the American Medical Association (Editorial, 1945, vol. 127, p. 1129), especially on the basis that it gives license to the unrestricted use of marihuana. They feel that sweeping and inadequate conclusions have been drawn on a narrow and thoroughly unscientific foundation. Possibly this controversy will be of value in stimulating further study of the whole problem. While it is possible to pick flaws in the report of the committee, its findings are entitled to a good deal of consideration.

O. R. L.

A Memoir to the Academy of Sciences at Paris on a New Use of Sulphuric Ether: 1847.

By W. T. G. MORTON. 24 pp. \$1.50. Henry Schuman, New York, New York, 1946.

This pamphlet should be of interest to all who have puzzled over the ether priority controversy of a hundred years ago. This is the first separate printing of the letter that was presented to the Academy by M. Arago, for Dr. Morton, in the Autumn of 1847.

H. N. H.

Quantitative Clinical Chemistry Interpretations. By JOHN P. PETERS and DONALD D. VAN SLYKE. Vol. I. 2nd Ed. \$7.00. 1041 pp. The Williams & Wilkins Company, Baltimore, Maryland, 1946.

The second edition of Peters' and Van Slyke's well-known work comprises a thorough revision of the text in order to bring it up to date. This is reflected by the increase in number of volumes to three, of which the first of two on "Interpretations" has been published. The principles which governed the making of the first edition in 1931 are adhered to in the present text, but, because of the tremendous bulk of information which is involved, the task of re-editing "Interpretations" has been performed by J. P. Peters while that for "Methods" has been accomplished by D. D. Van Slyke.

Otherwise, the content of the book is arranged similarly to that of the first edition and so requires little comment here. Attention should be called to the fact, not always appreciated, that "Interpretations" comprises an excellent reference text in the general field of biological chemistry. Its subject matter is extensive, the style lucid and the bibliography large. Emphasis is placed on the relation of various substances to disease, to action of drugs, and to general metabolism. In view of the fast developing prominence of physical and chemical knowledge in medical thought and the need for an extensive reorganization of medical education in keeping with it, this book can fill a much needed place at the elbow of every student of medicine, whether pre-graduate or post-graduate, whether interested primarily in clinical medicine or in some related field. While a convenient refer-

ence book, its subject matter does not permit it to be useful to someone who wishes a quick survey of some unfamiliar subject. On the other hand, it is not adequate by itself as a complete source of information for the individual who wishes to go deeply into some one field.

As a general appraisal, it may be said to fulfill its function admirably and to be of great use for persons of divergent needs. Perhaps the ideal book would approach these subjects from a more dynamic standpoint with more emphasis on both physical and organic chemistry, rather than on physiology and on substances as separate entities.

F. W. B., JR.

A Textbook of Clinical Neurology. By J. M. NIELSEN. 2nd Ed. Illus. 699 pp. \$7.50. Paul B. Hoeber, Incorporated, New York, New York, 1946.

This textbook is clearly written and concise. It contains a wealth of information and many illustrations. The author has written chiefly from his own experience and has not merely copied the material to be found in other texts. As one might expect, since the author has written so much on the subject of aphasias and related disorders, an interesting discussion of the cortical syndromes is included.

F. R. F.

Victory over Pain. By VICTOR ROBINSON. Illus. 338 pp. \$3.50. Henry Schuman, New York, New York, 1946.

Within the past few years there have been a number of books published on the history of anesthesia, five such appearing in 1945-46 alone. In *Victory over Pain* Dr. Robinson has presented this history in a most lucid manner in which fine diction has not served to obscure historical accuracy.

From its dark beginnings in antiquity the search of mankind for surcease from pain is traced through to the present. The text if not voluminous is certainly complete. Of particular interest is the author's mature presentation of the discovery controversy. It is made abundantly clear that the outstanding fact was that, following Morton's demonstration of anesthesia at the Massachusetts General Hospital in 1846, anesthesia came alive in the world. The role of those others who figured so tragically in the bitter altercation, Long, Wells and Jackson, is not minimized, but their accomplishments are evaluated in true perspective. As Dr. Robinson so eloquently puts it, "The four men did not meet in a tavern and pledge eternal brotherhood as the world rejoiced in the Victory over Pain. Alone they drank the wine of bitterness and tasted the lees of hatred. There was limitless glory for all, but not one would grant a share to another."

The biographic portrayals which comprise the bulk of the volume are well-drawn and charmingly delineated. It is a pleasure to see John Snow accorded the prominence he so rightly deserves for his contribution to anesthesia. Little heard of characters like Samuel Guthrie, backwoods scientist, country physician, powder-manufacturer and discoverer of chloroform; find their way into this account along

with Henry Hill Hickman who, unrecognized in his own time, understood the principles and practice of anesthesia. The subject is rounded out by a brief but adequate account of modern methods and masters.

All in all this is a thoroughly readable book. Although it will undoubtedly have wide appeal for the lay public, this should in no way detract from its appreciation by the professional man.

M. H. H.

Women in Industry: Their Health and Efficiency. By ANNA M. BAETZER. 344 pp. \$4.00. W. B. Saunders Company, Philadelphia, Pennsylvania, 1946.

The number of women in industry has increased so rapidly in the past years that some evaluation of the effect of such numbers of women on industry and of industry on the health and lives of women so employed is urgently needed. This book reviews the available scientific facts concerning the health and efficiency of women in relation to their employment, especially material gained during the war, and it attempts to point out those phases of the problem that need further investigation. In this analysis the performance of women has been compared with that of men on similar jobs and also the specific problems of women as women have been considered.

Despite immense gains made in the utilization of women during the war there are problems still not too well handled relating to the size, weight and fatiguability of women as compared with men. The necessity of fitting the conditions of the machine to the size of the worker seems to have been incompletely recognized. While women may become fatigued more readily than men, that seems to be attributable to household cares and responsibilities and to lack of background and adaptation to industrial work rather than to any specific factor of sex. Hours of work above the recommended forty-eight hours per week were found to increase the loss of time due to sickness, absence without permission, spoiled work and accidents, according to these impressive statistics. While absenteeism is greater among women than among men, when broken down, the evidence points to more frequent but shorter absences among women, possibly indicating a tendency on the part of women to take minor illnesses more seriously than men. On the other hand women have fewer industrial accidents. This may be due to difference in exposure, since the accident rate for women is higher for non-industrial accidents (exclusive of automobile accidents) than for men. It was found, however, that the higher rate of sickness in women was due to conditions common to men and women,—i.e. respiratory and digestive diseases.

In the realm of specific gynecological conditions it seems to be more difficult to interpret the evidence of the effect of industrial work on pregnancy, on premature births, on infant mortality and on maternal deaths. The social-economic factors which enter into these problems outside industry cannot be overlooked in their evaluation in industry. There seems to be less uncertainty about the type of work that pregnant women should undertake than how late in pregnancy a wo-

men should be allowed to continue her work. "Various federal and health agencies recommend at least six weeks antepartum leave and six to eight weeks postpartum leave with seniority rating undisturbed." Dysmenorrhoea in itself seems to be a relatively unimportant factor in absenteeism though I suspect from my clinical experience that it may be an undeclared cause of sick absenteeism more often than recognized. The menopause is said to be "unimportant in industry at present" and it is clear from statistics given here that older employed women tend to have many less absences than younger women. There are complicated social-economic factors present which prevent adequate comparison of these two groups. I agree with the author, moreover, that absenteeism among women can never be correctly compared with that among men until there is equal pay and equal opportunity for advancement, as only then will maximum output and maximal co-operation of women in industry be obtained.

Among the problems still requiring investigations to which attention is directed in this study are 1) the lower fertility record of women in industry; 2) the effects of certain processes—as lifting, reaching, vibration, heavy work, for instance, in causing or aggravating diseases of the pelvic organs; 3) the extent of occupational diseases and exposure to harmful chemical substances on women employed in industry and more especially the possible increased danger to pregnant women and to fertility; 4) the incidence of "strain and stress injuries" among women and whether there is more or less susceptibility to injuries of joints—such as tenosynovitis, bursitis or arthritis—resulting from vibration, friction or trauma; 5) accident rate in relation to hours of work.

There is excellent presentation of the benefits to industry as well as to the employee from improved personnel practices and also of the important role that the industrial physician may play in the field of preventive medicine.

There are an impressive number of charts giving statistical evidence in these and many other matters. For the first time there is here amassed a body of material that should make it possible hereafter to discuss the subject of "Women in Industry" with less repetition of generally accepted views without examination of the evidence on which these views were originally based." The researcher in the field of "Woman in Industry" will be deeply indebted to Dr. Baetjer for her skillful and careful analysis of so much pertinent material.

C. McC.

IDIOPATHIC LOW BACK PAIN AND SCIATICA— 25 YEARS AGO AND NOW*

J. ALBERT KEY, M.D.†

St. Louis, Missouri

By the expression "low back pain" we mean pain situated and originating in the lumbosacral region, that is at the level of the 4th and 5th lumbar vertebrae and sacrum, and which is not due to obvious disease or fracture of the vertebrae in this region. This is an area which can be covered by the hand of the examining surgeon, yet one which has been the subject of much careful anatomical and clinical investigation and of even more romantic speculation. This region has received unusual attention because pain and disability in the low back is one of the most frequent afflictions of mankind. This low back pain may or may not be accompanied by sciatica.

The mode of onset, intensity and distribution of the pain and clinical course of the condition vary greatly among patients presenting the symptom complex which we term "low back pain." In part it is this great variation in the clinical picture presented by these patients which has accounted for the multiplicity of theoretical explanations of the condition.

During the period when we were in school most of these low back pains were believed to be due to strains or subluxations or arthritis of the sacro-iliac or lumbosacral joints. As nearly as I can determine, the tendency to favor one or the other of the above joints was dependent largely upon the geographical location of the observer rather than upon any clinical or pathological evidence of disease in the given joint. In Boston under the influence of Dr. Goldthwaite, and here in Baltimore under that of Dr. Baer the sacro-iliac joint was the overwhelming favorite and practically all cases of low back pain which could not be explained by fractures, neoplasms, spondylolisthesis or destructive disease of the vertebrae were believed to be due to lesions of the sacro-iliac joints.

In a paper published in 1917, Baer (1) likened sacro-iliac sprains to

† From the Department of Surgery, Washington University, St. Louis, Mo.

* Read before the Johns Hopkins Medical and Surgical Club, Feb. 27, 1947.

sprains of the ankle and stated that the ligaments holding the sacrum to the ilium could be wrenched, causing a strain or sprain of the sacro-iliac joint. Depending upon whether the sacrum was tilted backward or forward they were divided into types A and B. The type A sprain was characterized by a flat back and unilateral lumbosacral pain and often it was accompanied by referred pain in the distribution of the superior gluteal and sciatic nerves. It corresponded to the traumatic type of lumbosacral strain of other authors (Key (2)) and the type B sprain with hollow back and bilateral lumbosacral pain which was not referred was similar to the postural type of lumbosacral strain. It was stated that the diagnosis was quite simple and that lumbago is generally a strain of the sacro-iliac joint.

Those who believed that the pain originated in the sacro-iliac joints studied the anatomy and physiology of these joints and presented convincing arguments in support of the vulnerability of these joints to strain or subluxation and of the tendency of such injuries to cause pain in the distribution of the sciatic nerve either as referred pain or by direct irritation of the nerve roots as they crossed the joint. Smith-Petersen and Rodgers (3) studied the articular cartilage from some of the sacro-iliac joints and reported end results on 26 patients who were subjected to sacro-iliac arthrodesis for the cure of low back pain and sciatica. Some of the specimens exhibited evidence of traumatic arthritis, and the symptoms were relieved by the operation in 22 of the 26 patients, and were partly relieved in two others. Even more spectacular are the results reported by Baer (1). In the severe cases with marked disability and sciatic pain he advised manipulation under full anesthesia followed by immobilization for 10 days in a short plaster spica. The manipulation consisted of passive flexion of the affected hip with the knee straight, to well beyond 90°. This stretched the hamstring muscles and was believed to move the ilium backward on the sacrum and thus reduce the subluxation. Baer (1) stated that he had "manipulated 100 of these cases by this simple method with immediate relief in almost every case, and with a relapse in only three."

It would thus seem that the problem of low back pain and sciatica was solved satisfactorily 30 years ago. Indeed Baer stated "I know of no class of cases where the results obtained are so pleasing, both to the patient and to his physician." Unfortunately, neither the manipula-

tive treatment nor the arthrodesis nor even the incrimination of the sacro-iliac joint as the seat of the trouble has stood the test of time. Danforth and Wilson (4) in 1924 after careful anatomical studies of the low back and clinical observations on 21 patients, concluded that "the sciatic pain of the type studied is a symptom of disturbance in the lower lumbar spine and that the site of the lesion is most frequently in the lumbosacral junction and the nerve chiefly involved is the 5th lumbar."

As more orthopedic surgeons realized that they were failing to relieve many of their patients with low back pain and sciatica by therapy directed at the sacro-iliac joint their attention was shifted to the lumbosacral joints and braces were devised for their support and operations were performed for lumbosacral fusion (Williams (5)). The lumbosacral region offered an especially fertile field for speculation because congenital anomalies occur here more frequently than they do in any other part of the skeleton and in addition to the strains, subluxations and diseases which any joint might be heir to, this region presented a large number of anatomical variations which were thought to account for much of the pain originating in the low back. This was especially true of enlarged or partly sacralized transverse processes. Just as in the case of the sacro-iliac joint series of cases were reported in which low back pain and sciatica were relieved in almost every case by lumbosacral fusion.

However, this method too did not stand the test of time and many orthopedic surgeons were not satisfied with the results which they and their colleagues were obtaining in these cases. Having noted that the sciatic pain disappeared in a patient whose fascia lata he had divided for the correction of a flexion deformity of the hip, Ober (6) quickly convinced himself and many others that idiopathic low back pain and sciatica were caused by a tight iliotibial band and a great many patients were subjected to the operation of fasciotomy and many were reported to have experienced relief after the operation.

Again time proved that fasciotomy was not a panacea for low back pain and the operation was gradually abandoned, and the great majority of orthopedic surgeons continued to treat these patients conservatively. The type of conservative treatment depended upon whether or not the patient was so disabled that he was confined to his home or

preferably to a hospital. If so he was kept in a bed with a firm mattress and a fracture board beneath the mattress and a small pad or pillow beneath the lumbar spine and a moderate amount of traction might be applied to one or both legs. This was supplemented with local heat and sedatives as necessary for the relief of pain.

Other surgeons insisted that the lumbar spine should be maintained in flexion and the head and shoulders and knees were elevated. These patients were also subjected to various types of manipulation either with or without anesthesia and these manipulations might be repeated as often as seemed indicated. In some instances the spine was immobilized in a plaster of paris jacket or spica cast.

Ambulant patients were given support to the low back in the form of adhesive strapping, belts, corsets, plaster jackets or braces, and were advised to avoid subjecting the back to unusual strain, to avoid fatigue and to sleep on a firm bed with a fracture board beneath the mattress. They were given postural exercises and stretching exercises and the shoes were altered if this seemed indicated.

In addition to the above, physical therapy, especially local heat and massage and various types of manipulation without anesthesia were used to a variable degree. In any patient with acute low back pain the low back might be strapped firmly with adhesive, the strapping extending from the level of the trochanters upwards to grasp the lower ribs. This often afforded considerable relief whether the patient was confined to bed or ambulant, but precluded the use of local heat or massage.

In addition to the methods mentioned above, injections of novocaine into the lumbosacral region or into so-called trigger points, or epidurally through the sacral canal have been used extensively and such injections have been reported to have cured a high percentage of the patients in which they were used. Others injected air beneath the lumbar fascia and likewise reported that the patients were relieved of their symptoms.

Other reported causes of the low back pain and sciatica in a small percentage of cases were pressure by the pyriformis muscle on the sciatic nerve, adhesions or bands in the sacral canal especially in patients with spina bifida occulta, hypertrophied asymmetrical articular facets compressing one or more nerve roots, enlarged transverse proc-

esses pressing on a nerve root, kissing spinous processes or herniations of fat through the deep fascia, and it has been reported that surgical procedures directed at the removal of each of the above causes has resulted in the relief of the pain and disability in the patients who were operated upon. Finally in 1934 Mixter and Barr (7) published observations on a series of patients in whom protrusions of intervertebral discs had pressed upon the roots of spinal nerves and had caused pain in the low back and sciatic nerves and in some patients had also caused sensory and motor paralysis of such a degree that it could be detected upon neurological examination. They further showed that the protruding disc could usually be localized by spinograms after Lipiodol had been injected into the subarachnoid space, and that relief of the symptoms followed the surgical removal of the protruding disc.

It was immediately recognized that Mixter and Barr had made an important contribution to our knowledge of the cause and treatment of low back pain and sciatica and neurological surgeons accepted their work with enthusiasm and aggressively attacked the problem as it presented a new field for their surgical activities.

Orthopedic surgeons on the other hand who had been dealing with low back pain and sciatica for many years and had seen most of these patients get well under a wide variety of diagnoses and because of or in spite of many different forms of conservative and operative treatment were willing to admit that in a small percentage of the cases which presented the typical syndrome of low back pain with sciatica with neurological disturbances the symptoms might be due to protruding intervertebral discs, but they believed that the great majority of these cases were suffering from strains of subluxations or arthritis of the lumbosacral or sacro-iliac joints and they continued to treat these patients conservatively or by manipulation or fusion of the suspected joints. Especially did orthopedic surgeons object to the injection of Lipiodol into the subarachnoid space as they feared that this might cause meningeal irritation and add to the patient's trouble.

When Dandy (8) and some other surgeons had become sufficiently familiar with the clinical picture and operative findings in patients suffering from protrusions of intervertebral discs in the lumbosacral region to permit them to operate upon these patients without subjecting them to the injection of radio-opaque material into the subarach-

noid space, interest in these lesions broadened and evidence accumulated which indicated that lesions of the intervertebral discs were the most frequent causes of idiopathic low back pain. Key (9) stated that "the symptoms which we formerly attributed to sacro-iliac or lumbosacral strain, arthritis or subluxation, lumbosacral facet syndrome, postural strains of the low back, and myofascitis or fascitis in the lumbar region are really due to lesions of the intervertebral discs in this area." In a second provocative paper read before the 1944 meeting of the Southern Surgical Association, it was concluded that the conditions which we have called low back strains and classified as idiopathic low back pain are lesions of intervertebral discs in this area" (Key (10)).

When they were presented each of the above papers was subjected to considerable adverse criticism. Their contents were very much in line with opinions expressed by Walter Dandy (11) who has contributed so much of lasting value to our knowledge of intervertebral disc lesions. Almost three years after the above papers were written I am even more convinced that the apparently radical statements which they contained are correct. This opinion is based on the following:

1. In a high percentage of a relatively large series of personally studied and operated cases (about 400) in which the diagnosis was obtained from the history and physical and x-ray examination the pre-operative diagnosis was proven to be correct when the spinal canal in the lower lumbar region was explored at the operation. Most of these patients were not subjected to spinograms before the operation and it was not possible always to localize the offending disc or discs with precision before the operation, but this was done by inspection and palpation at the operation. The suspected disc was exposed and if this appeared normal or not sufficiently abnormal to account for the symptoms the adjacent disc was exposed and examined. A satisfactory percentage of these patients are improved or relieved after the operation.

2. In many of these cases the patients were followed or seen at intervals over periods of months or years before they were operated upon and some of them were subjected to long continued conservative treatment. Over a period of time a given case might present various gradations between a normal back with no symptoms and a rigid flat back with a contra-lateral list and severe unilateral pain in the low back

which extended into the buttock and down the course of the sciatic nerve to the foot and this might be accompanied by sensory disturbance and loss of the ankle jerk on the affected side. The fact that in a given patient the clinical picture may vary so greatly from week to week or from day to day has not been sufficiently emphasized in the study of this condition.

3. In a large series of patients presenting the syndrome of idiopathic low back pain all gradations may be found between the patient who complains of occasional mild bilateral or midline lumbosacral pain which is not referred and is present only when he is tired and who is normal on physical and laboratory examinations and the patient who is completely disabled by severe low back pain and sciatica and who on physical examination presents the typical picture of a protruding intervertebral disc in the lumbosacral region. These variations of the pain among different patients in a series of patients with low back pain or from time to time in a given patient are explained more satisfactorily by an injured or diseased and protruding intervertebral disc than by any other pathological condition which is known to occur in the low back. And this opinion is confirmed by the patients who come to operation and in whom the protruding disc is found and removed and this is followed by relief of the patient's symptoms.

4. I have operated upon a moderate number of patients whose complaint was bilateral or midline pain in the lumbosacral region which was not referred, but was sufficiently troublesome and resistant to conservative treatment to warrant operation. These patients correspond to the group described by Dandy (11) as recurring low back ache without sciatica. Figures 1 and 2 reproduce a spinogram of such a case. This man had suffered from severe bilateral lumbosacral pain for several years and at no time had the pain radiated to either buttock or lower extremity. At operation a soft, fluctuant, dome-like, protruding disc was found in the midline at the 4th lumbar interspace as shown in the myelogram. However, since this man's local tenderness had been especially marked over the 5th lumbar disc, this also was examined and it was found that this disc was soft, fluctuant, dome-like, and protruded in the midline even more than did the 4th disc. This was not shown in the myelogram. Both protruding discs were removed and the patient made a rapid and complete recovery and writes



FIG. 1. SPINOGRAM OF PATIENT WITH CHRONIC BILATERAL LUMBOSACRAL PAIN WITHOUT SCIATICA. ANTERO-POSTERIOR VIEW, INDICATING MIDLINE PROTRUSION OF THE 4TH LUMBAR DISC

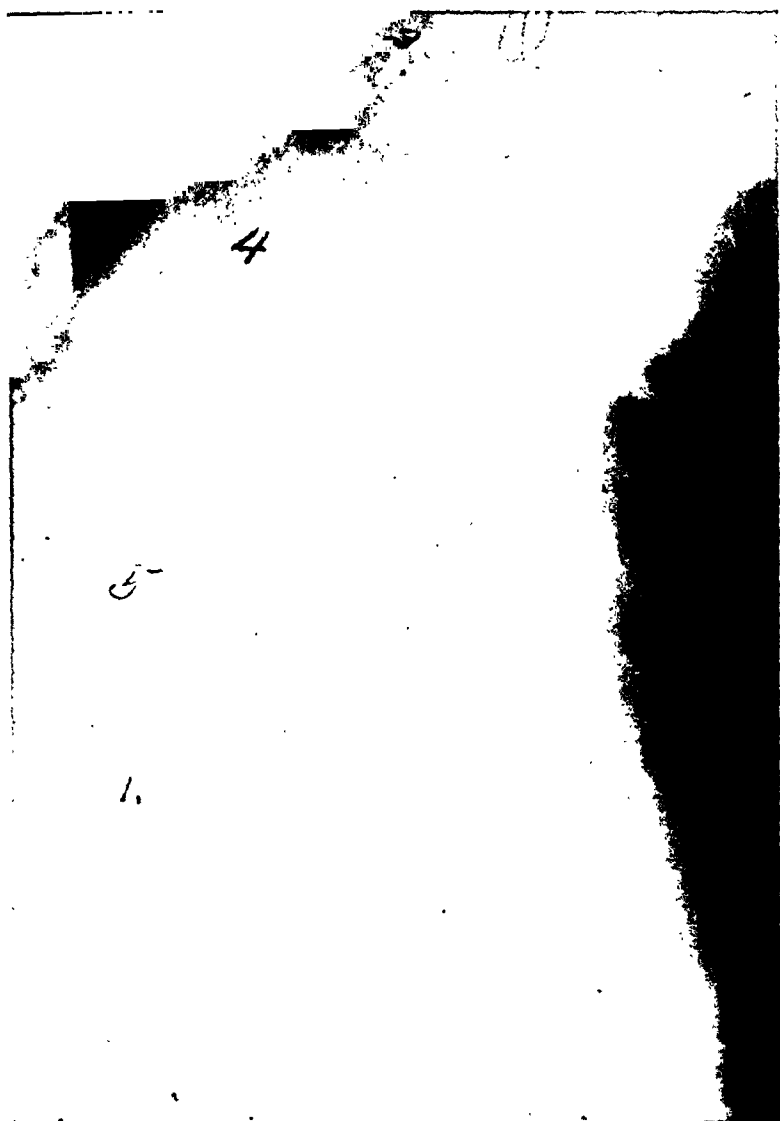


FIG. 2. SAME PATIENT—LATERAL VIEW, SHOWING PROTRUSIONS OF 3RD AND 4TH DISC

At operation a larger protrusion was found at the 5th disc which was tender before operation. Both 4th and 5th discs were removed and the patient's symptoms were relieved. The 3rd disc was not disturbed.

that he is having no pain in his low back. This patient and the myelogram thus prove three of the statements for which Dandy was criticized. These are:

- a. Midline discs occur and may cause low back pain without sciatica.
- b. The concealed or hidden discs may occur and cause symptoms, and
- c. The myelogram may fail to show a protruding disc.

5. Failure of the myelogram to reveal a protruding disc is not conclusive evidence that such a disc may not be causing pain. Since we have learned to remove the pantopaque, Dr. Lee T. Ford and I have been using larger amounts of the radio-opaque material (9 to 15 ccm.) and studying the outline of the spinal canal with the patient standing as well as in various positions in recumbency. Even with this technique we have occasionally found errors in the myelograms, but the percentage of correct diagnoses by myelography which were proved at operation is relatively high.

6. The other alleged causes of idiopathic low back pain and sciatica are not based upon any proven pathological lesions. The ruptured or protruding intervertebral disc is the only pathological lesion which has been demonstrated to cause idiopathic low back pain and sciatica. When the disc material removed at operation was subjected to microscopic examination, degenerative changes were noted in about 50% of the specimens from a group of my cases (Eckert and Decker (12)). However, there was no correlation between the microscopic picture of the specimens and the symptoms or result obtained by the operation. This is to be expected if the symptoms are due to mechanical pressure or strain or to inflammation caused by these factors. When at operation the pain is found to be caused by pressure of an unrecognized metastatic carcinoma on a nerve root as occurred in two of my cases or to a tumor in the spinal canal as occurred in one of my cases the case is no longer one of idiopathic low back pain.

7. Failure to cure the patient by operation for removal of the offending disc is not acceptable evidence that a lesion of an intervertebral disc was not the cause of the pain. The offending disc may not have been found and removed or more disc material may have been extruded from the incompletely removed disc or a second protruding disc may be contributing to the patient's symptoms.

8. The fact that the symptoms may be relieved or not affected or made much worse by manipulations either without or with anesthesia is best explained by the possibility that the position of protruding disc material or of the nerve root may have been shifted by the manipulation. Can one imagine a sprained ankle or wrist being relieved by forcible manipulation? And in the case of the discs it makes no difference whether the manipulation was directed at the sacro-iliac joints, the lumbosacral joints or the lower lumbar discs, because it is not possible to manipulate one of these structures without applying force to the others in approximately the same degree.

9. The further fact that some patients who are temporarily relieved by manipulations gradually become worse after repeated manipulations and either suddenly or slowly arrive at a state where surgical removal of the protruding or extruded disc material is necessary if the patient is to be relieved of the pain is best explained by a disc lesion. All of us who deal with these patients have seen many of them with severe disc lesions who have been subjected to prolonged and repeated osteopathic or chiropractic manipulations for a low back pain which in the beginning was relatively mild and in no sense a condition for which operative treatment would be considered. I believe that the eventual severe disc lesion in many of these cases is caused by the repeated manipulations and that many disc operations would be avoided if rest and support to the low back were substituted for manipulation in the early or mild cases.

There is no doubt but that a high percentage of these disc lesions heal or at least the symptoms subside spontaneously.

It thus appears that in a patient suffering from low back pain with or without sciatica the first problem is to determine whether or not the pain originates in the low back. Usually this can be done by the history and physical examination. It is to be noted that the examination must be made while the patient is having pain or at least symptoms, otherwise it is apt to yield little information and it may be necessary for the patient to return one or more times for re-examination before it can be determined that the pain originates in the low back. Then if the x-ray reveals no evidence of spondylolisthesis or fracture or destructive disease or ankylosing arthritis the patient is assumed to be suffering from idiopathic low back pain and the burden of proof is on him

who says that this is not caused by a lesion of one or more of the intervertebral discs in this area.

The patient should then be treated conservatively along the lines mentioned in preceding paragraphs until he is relieved or until it is determined that his symptoms will not yield to conservative treatment and that they are sufficiently troublesome to justify a major surgical operation. Not until it is decided that operative treatment is indicated should he be subjected to a spinogram. This should be done when the surgeon desires to localize the protruding disc precisely before the operation and not for the diagnosis of a disc lesion. As much pantopaque as is considered advisable should be injected and this should be removed after the examination is completed. In my experience a spinogram is rarely necessary even in cases which are to be operated upon.

Even when the spinogram fails to reveal a protruding disc the operation for exploration of the canal and search for and removal of the offending disc should be performed if the patient's continued pain and disability justify the procedure.

Surgical treatment is reserved for those cases which fail to yield to conservative treatment and I wish that it were possible to state that the surgical removal of protruding discs will cure all of these patients with idiopathic low back pain. Unfortunately, there is a small group of not over 5% who are not helped by the operation and another group of about 20% who are only partly relieved. In the other 75% the results are very satisfactory.

It thus appears that in the treatment of idiopathic low back pain our best results today do not compare favorably with those obtained 25 years or more ago when many of these patients were treated by manipulations directed at the sacro-iliac joints or later by any one of several methods. For instance Baer's report indicates that he cured 97% of his cases by a simple manipulation of the sacro-iliac joint under anesthesia followed by immobilization for 10 days in a plaster cast. And now 30 years later we have abandoned that relatively simple procedure because we have found it ineffective and resort to a difficult major surgical operation and can cure only about 75% of the cases which we operate upon.

This apparent lack of progress is partly explained by a probable difference in the type of cases which comprise a given series. It is well

known that a large percentage of the patients with low back pain recover spontaneously without treatment or under a wide variety of methods of treatment. It is probable that most of the cases included in the earlier series would now get well under conservative treatment for the relief of idiopathic low back pain and we reserve our operative treatment for the small percentage of this large group of cases which suffer repeated or continued pain and disability and fail to respond to conservative treatment. It is our hope that with more experience the operative treatment may be improved to a point where our results will be even more satisfactory than they are now. It may be that in the next quarter century we will learn some other and more satisfactory solution to the problems presented by these lesions of the intervertebral discs. In the meantime we wish to emphasize the fact that a diagnosis of an intervertebral disc lesion does not mean that the patient should be operated upon and the offending disc or discs removed. The patient should first be treated conservatively and if this fails then the operation can be performed with a fair chance that it will be followed by relief of the pain. In my experience lumbosacral fusion is rarely necessary if the offending disc has been removed.

1. BAER, WM. S.: Sacro-Iliac Strain. *Bulletin of the Johns Hopkins Hospital*, 1917, 28: 159.
2. KEY, J. ALBERT: Low Back Pain as Seen in an Orthopedic Clinic. *Am. Journal Med. Sci.*, 1924, 168: 526.
3. SMITH-PETERSEN, M. N., AND ROGERS, WM. A.: End-Result Study of Arthrodesis of the Sacro-Iliac Joint for Arthritis—Traumatic and Non-Traumatic. *Journal of Bone & Joint Surgery*, 1926, 8: 118.
4. DANFORTH, M. S., AND WILSON, P. D.: The Anatomy of the Lumbosacral Region in Relation to Sciatic Pain. *Journal Bone & Joint Surgery*, 1925, 7: 109.
5. WILLIAMS, P. C.: Reduced Lumbosacral Joint Space; Its Relation to Sciatic Irritation. *Journal of the American Medical Association*, 1932, 99: 1677.
6. OLF, F. R.: Relation of the Fascia Lata to Conditions in the Lower Part of the Back. *Journal of American Medical Association*, 1937, 109: 554.
7. MINTLE, W. J., AND BAER, J. S.: Rupture of the Intervertebral Disc with Involvement of the Spinal Canal. *New England Journal of Medicine*, 1934, 211: 210.
8. DANDY, W. E.: Concealed Ruptured Intervertebral Discs: a Plan for the Elimination of Contrast Mediums in Diagnosis. *Journal of the American Medical Association*, 1941, 117: 84.

9. KEY, J. ALBERT: The Conservative and Operative Treatment of Lesions of the Intervertebral Discs in the Low Back. *Surgery*, 1945, **17**: 291.
10. KEY, J. ALBERT: Intervertebral Disc Lesions are the Most Common Cause of Low Back Pain with or without Sciatica. *Annals of Surgery*, 1945, **121**: 544.
11. DANDY, W. E.: Treatment of Recurring Attacks of Low Back Ache without Sciatica. *Journal of the American Medical Association*, 1944, **125**: 1175.
12. ECKERT, C. L., AND DECKER, A. M.: Pathological Changes in Intervertebral Discs. To be published in *Journal of Bone & Joint Surgery*, 1947.

THE ORIENTING REFLEX (QUESTIONING REACTION): CARDIAC, RESPIRATORY, SALIVARY AND MOTOR COMPONENTS

JANICE ROBINSON AND W. HORSLEY GANTT

Partition Laboratory of the Phipps Psychiatric Clinic, Johns Hopkins University

In the functional study of the nervous system by the methods originated by Pavlov the quantitative ideal has determined the direction of many investigations. Some of the less readily measurable, or more complex, responses have thus suffered comparative neglect, in spite of their fundamental importance.

The purpose of this paper is to report in some quantitative detail upon a study of certain aspects of one of these complex behavior patterns—the one which has been variously called by Pavlov the “orienting reflex,”¹ the “investigatory reflex,” the “focusing reflex.”

In the description which Pavlov has given one will recognize a fundamental reaction pattern presented by a wide range of animals in reaction to a sudden change in the environment. The complexity and variability of this behavior pattern to a sudden new “stimulus” invites a corresponding variety of designations depending upon the aspect of the behavior which catches the observer’s interest and attention. Pavlov, in “focusing” his attention upon the investigative behavior of his dogs aptly used the term “investigatory reflex.” There is, however, a preliminary phase of the reaction in which investigatory behavior has not yet clearly crystallized—a phase which might be designated “questioning reaction” or, by Pavlov’s own term, the “what-is-that reflex.”

HISTORICAL

Pavlov first described in 1910 the reaction of the animal to a new stimulus as the “orienting or focusing reflex”; he considered it as a disturbance producing external inhibition of the conditional reflex (abbreviated *cr*).

“Every sound, be it ever so small, appearing in the midst of habitual sounds and colors which surround the dog, each weakening or reinforcing of these constant

¹ All revised *OR*.

sounds, each change in the intensity of the room illumination (the sun becoming hidden by the clouds, a sunbeam suddenly breaking through, a flickering of the electric lamp, a shadow across the window), the appearance of a new odour in the room, a warm or cold current of air, something touching the skin of the dog, as a fly, or a falling speck of plaster from the ceiling—in all these and in endless like cases, there fatally begins an activity of one or another of the skeletal muscles of our animal, as of the eyelids, eyes, ears, nostrils; or the head or the trunk or some other part of the body will turn and take a new position; and these movements are either repeated and reinforced, or the animal becomes fixed in a certain pose.

"We have before us again a special reaction of the organism, a reflex of the simple kind which we call an *orienting* or *focusing* reflex. If in the surroundings of the animal there appears some new agent (by this I include changes in the intensity of previously acting agents), then the corresponding receptor surfaces of the organism become focused on it, in a manner which will bring about the most favourable stimulation." (Pavlov, "Lectures on Conditioned Reflexes," vol. I, N. Y. 1928, p. 134.

Any change in the environment—tactile, olfactory, auditory, visual—may elicit the OR. If the stimulus is too strong, instead of the OR there may be a startle reflex, or some marked emotional state as fear. A characteristic of the OR is that it tends to disappear with repetition, as the animal becomes accustomed to it.

In 1916 in the lecture *Reflex of Purpose* Pavlov added the word "investigatory reflex" and considered this reaction the basis of inquisitiveness, scientific research, etc.

"Now every new factor arising in the surroundings, if repeated at short intervals and unaccompanied by any further direct influence on the animal, becomes more and more indifferent. The orienting reflex which it calls out becomes weaker and finally disappears, and with it also disappears the inhibitory action on our conditioned reflex. On this extinction is based the fact that the constant composition of the surroundings remains without apparent effect on the animal." In addition to the orienting reflex: "All extremely strong stimuli, strong light, sudden noises, etc., provoke special reactions, as, for example, shivering or trembling of the animal, the reaction of running away, trying to break away from his stand, or the opposite cataleptic-like state; on the other hand, the sight and sound of persons having a certain relation to the experimental animal, or the sight and sound of other known animals, and various things of the same sort, condition every previously elaborated response on the part of the animal" (1).

The OR is often difficult to demonstrate unless other extraneous stimuli are excluded. Thus in an animal running about one may not see a reaction to new stimuli or even to loud noises, whereas in the experimental camera, one may usually see the animal or person turn his head to the slightest sound, light or tactile stimulus.

Pavlov noted that the OR inhibited both the excitatory cr (external inhibition) and the inhibitory cr (disinhibition) and it was to avoid such interferences that he built a sound proof camera.

For purposes of observation and reporting in this paper we use the term "orienting reflex." Whitehorn has suggested tentatively the use of the terms "questioning reaction," or "uncertainty reaction" thus stressing that aspect or phase of the reaction which was indicated by Pavlov's term "what-is-that" (Russian *shto takoe*) reflex. This aspect was emphasized by a student in this laboratory, unfamiliar with either the term or the reaction, who seeing it for the first time, said, "the dog looks as if he is asking a question."

In subsequent studies, it may prove useful to discriminate different phases by different terms.

By several criteria the OR may be considered an unconditional response; it occurs in many species, it is inborn and present without training, and it persists after ablation of the cortex. The peculiarity of the OR lies in the fact that in the intact animal it disappears or weakens after repetition of a given stimulus. Perhaps this characteristic could be more aptly expressed by saying that the stimulus to elicit a "questioning reaction" in a normal animal, must be continually new and different. The disappearance or weakening of the "questioning reaction" on repetition of the same stimulus may be considered as an instance of cortical or conditional inhibition, since such weakening does not occur in a decorticated animal. The "questioning reaction" may include as an element the startle reflex although it is not identical with this reflex.

The progressive decrease in intensity of the OR, i.e., its gradual extinction by repetitions of the same stimulus without the reinforcement provided by novelty, may be considered an adaptive process, but the exact extent and rate of its progress has not been measured heretofore owing to the lack of an adequate method. Pavlov studied this inhibition of the OR by simply observing the disappearance of the

motor investigatory components, and he also made attempts at quantitative study through measurements of the inhibiting effect of the OR on other conditional reflexes.

The study here reported is related to studies on cardiac conditional reflexes previously conducted in this laboratory.

In 1934 E. C. Andrus and Gantt began to study the possibility of forming cardiac conditional reflexes to peripheral nerve stimulation, and in 1939 Hoffmann and Gantt and in 1942 Dworkin and Gantt established the fact that the heart rate changed regularly during the action of a conditional stimulus signaling either food or pain—in other words that there is a definite cardiac conditional reflex subject to general laws of learned behavior (2).

In further quantitative studies of cardiac reactions it has become necessary to learn how much of the animal's measured cardiac response to a conditional stimulus is a result of the conditioning process and how much might be attributable to the new stimulus itself (i.e. a part of the orienting reaction).

For these several reasons we have undertaken to investigate the normal course of reaction to a new stimulus. We have also compared the reaction to such a stimulus (both before and after the animal has become accustomed to it) with the reaction to the same stimulus after it has been made the conditional stimulus for some other specific reflex.

METHOD

Seven dogs were used in these experiments, six of them never having been worked with previously in the laboratory. The fact that Gosha and Connie had been fed in the experimental camera may have influenced some of the results. After a dog was well accustomed to the experimental environment, it was placed repeatedly in the experimental camera and a stimulus was given (tone, metronome, buzzer or light). These specific stimuli had not been used for any previous conditioning of these animals (except Connie, as noted below) nor were these stimuli, in this phase of the study, reinforced, that is, given in association with an unconditional stimulus for specific reflexes, such as ordinarily serves to establish a conditional reflex. Ten to forty repetitions of the new stimuli acting for 30 seconds were given on each

TABLE I

Gosha, 24 November 1944

Showing the reaction of the dog to neutral auditory stimuli (M40, Bu) beginning with the first time they were used

In the column "Control" the HR is given for the 10" period immediately preceding the stimulus. In the "Cardiac OR" there are given in sequence the HRs for every 5" while the auditory stimulus is acting. The italics in this column indicate that there is during the period of the italicized figure a motor component of the OR. The next column "UR" indicates the cardiac rates to the eating of 10 gms. of food taken every 5" after the beginning of eating. The bold figures in this column show that the dog is in the act of eating for the period that these rates are taken. When the dog is licking the food box but not eating a star is placed beside the HR for that period. The last column "Interval" contains the HRs for 5" periods immediately following the 30" after the beginning of eating, or after the cessation of the auditory stimulus.

TIME	STIM.	NO. REF.	CONTROL	CARDIAC OR Q 5"						UR (10 GMS. FOOD)						INTERVAL Q 5"									
				0-5"	5-10"	10-15"	15-20"	20-25"	25-30"	0-5"	5-10"	10-15"	15-20"	20-25"	25-30"										
14:54	M40	1	74	106	106	82	79	84	98							92	77	83	78	79	77				
14:59	Fd.	—	77							134	138	114	86	82	78							73	82		
15:01	M40	2	83	94	114	85	74	73	88							77	88	78	72	78	73	77	77		
04	M40	3	70	82	80	73	77	77	73							66	71	78	72						
07	M40	4	74	84	94	118	108	96	88							68	73	94	78	76					
10	M40	5	73	83	78	70	74	74	70							83	73	79	62						
12	M40	6	73	80	74	74	64	72	73							66	68	86							
15	M40	7	74	90	94	90	97*	102*	78							74	74	62	73	70					
17	Bu	1	73	91	133	107	86	94	82							73	67	72	64						
19	Bu	2	67	72	93	91	87	97	88							80	74	74	79						
21	M40	8	80	84	77	101	94	77	71							85	64	66	64						
23	Fd.	—	62							124	131	110*	89*	96*	80	—	—	—							
27	M40	9	69	72	84	77	78	78	78							70	72	71	61						
30	M40	10	69	73	82	72	76	70	73							72	73	60	70						
32	M40	11	68	70	80	90	90	95	72							69	60	67	68	59	70	74			
35	M40	12	66	77	78	74	60	71	68							69	58	72	64						
38	Fd.	—	85							132	132	118	96	98	86	86	92	96	85	80	84	76			
41	M40	13	75	91	90	90	82	83	89							90	104	83	94	79	76	71	74		
44	M40	14	72	76	72	67	78	73	77							85	73	65	74						
47	M40	15	68	74	73	67	73	68	86							65	71	74	77						
49	M40	16	70	79	74	68	70	71	106							125*	93	84	79	82	76				
52	Bu	3	72	78	79	72	72	71	74							68	66	66	62	65	67				
54	Fd.	—	72							120	138	98	82	82	78		96	84	80	78	91	136	132		
58	M40	17	77	95	92	88	89	79	84							85	77	83	94	84	82	76			
16:01	M40	18	77	82	84	84	80	85	88							89	74	89	97	82	83				
03	M40	19	83	86	—	—	—	82	91							93	94	98	68	82	88	67			
08	M40	20	75	77	97	79	77	72	84							82	71	66	71	67					
12	M40	21	75	88	68	84	96	83	73							72	95	83	83	62					
16	Bu	4	72	82	74	72	76	74	77							75	70	77	73	67	72	66	70	71	68
18	Fd.	—	77							121	120	89	88	77	91		95	74	73	74	72	76	79	74	78
21	Bu	5	70	84	88	83	77	73	74							72	76	66	67	70	71	68			
24	Bu	6	67	83	84	79	70	74	79							68	72	68	71	66	78	88			
26	M40	22	80	88	76	80	88	82	92							77	74	79	77	84	100				
29	Bu	7	70	79	74	72	74	82	60							72	72	76	67	76	72	71	70	74	
36	Fd.	—	70							106	122	84	86	74	91		85	77	85	86	98	73	94		
Av.	M40		73	83	84	82	81	79	82	123	130	102	87	85	84	80	76	77	74	76	80	80	80	72	74
	Bu		70	81	89	82	79	80	76																
S.D.	M40		5.1	8.7	10.7	12.7	11.6	8.6	10	10	7.7	14	4.8	10	6.2										

of three or four days at intervals of a few minutes until no marked changes (motor, cardiac, respiratory) occurred to the stimulus, or such changes were relatively constant. The reactions of the animals to the new stimuli were carefully noted—heart rates, duration and strength of motor ORs, latent periods,—and in two animals with chronic fistulae of the parotid gland, the salivation to the stimuli was measured. The heart rates were recorded with a Brush Oscillograph or a Parmenter Cardi tachometer and counted for 5 second periods as shown in Table I.

Gosha, a young active female Pit bull terrier was first brought into the laboratory 30 December 1943 and accustomed to the camera by bringing in and feeding it several times a week from the food box. (The early experiments were performed by Evelyn Whitehorn.) The dog was not brought into the camera again from 2 February 1944 until the 27 October 1944. It was brought into the camera 6 times for feeding between the 27 October 1944 and 24 November 1944, on which date the neutral stimuli (M40 and Bu) were introduced for the first time.

The dog was seen through a glass window of the camera separated from the experimenter. The time after the beginning of the stimulus when he turned or made any movement directed in a definite direction about the source of the stimulus was recorded as the latent period of the OR; the duration of this movement as well as its estimated intensity was also noted.

OBSERVATIONS

I. Motor Component of the Orienting Reaction. Ordinary observation of the OR is at best a rough estimation influenced by the experience and attitude of the observer. In this laboratory we evaluate the intensity of the dog's motor reaction (pricking of ears, turning to source, vocalization) on a four-point scale of intensity—a single plus (+) signifying a barely perceptible response, four plus (++++) an extremely strong response and ++ and +++ appropriate gradations ranging between.

In spite of the difficulties of evaluation involved, the pattern of change in the motor reaction was generally recognizable and paralleled roughly the extinction of the cardiac component of the reaction. The most marked reaction occurred the first time the stimulus was given,

and progressively diminished upon repetition during each session, and was found to be of low intensity even at the beginning of each new session, unless a long time intervened. A marked strengthening of the motor OR to a specific stimulus occurred for some minutes after food was given in the camera.

This pattern of extinction was followed in all dogs except Clare, whose motor reactions increased in intensity from day to day. Until more evidence is accumulated on a large number of animals, it is of course impossible to draw conclusions about Clare's deviation from the usual course of the OR and its relation to her hyperreactivity later in the camera (which was so violent as to make her unsuitable for laboratory work).

Duration of the motor investigatory behavior is as difficult to estimate as strength, and does not follow any clearcut pattern. On the whole, however, it may be said that with repetition a definite trend of diminishing duration of the OR was perceptible in our dogs, the duration becoming shorter as the apparent "tension" of the dog's movements decreased.

The latent period of the motor OR is subject to the error of unaided observation. There is a large margin of error depending upon the judgment of the individual observer. This index was of little value in the present study. In general the stronger the motor components of the OR the shorter the latent period. But the latent period is not only a characteristic of each observer but of each individual dog as well as of the kind of stimulus used.

II. Salivation and the OR. There appears to be no special reason, a priori, why salivation should be considered a component of the OR, and our observations are not consistent with such a formulation, for there is little evidence of quantitative parallelism between salivary secretion and the OR; yet we have observed remarkable instances of some kind of a relationship. The stimulation of salivation by food or by conditional stimuli may markedly enhance the OR to a new stimulus, or revive an OR to a particular stimulus previously extinguished by repetition. Furthermore, in an experimental camera which has been used for salivary experiments, a new stimulus may elicit, along with the OR, a strong salivary response.² Some of the details

² The question remains undecided as to whether this so-called salivary component in Gosha is such a generalised conditional reflex in its incipient stage.

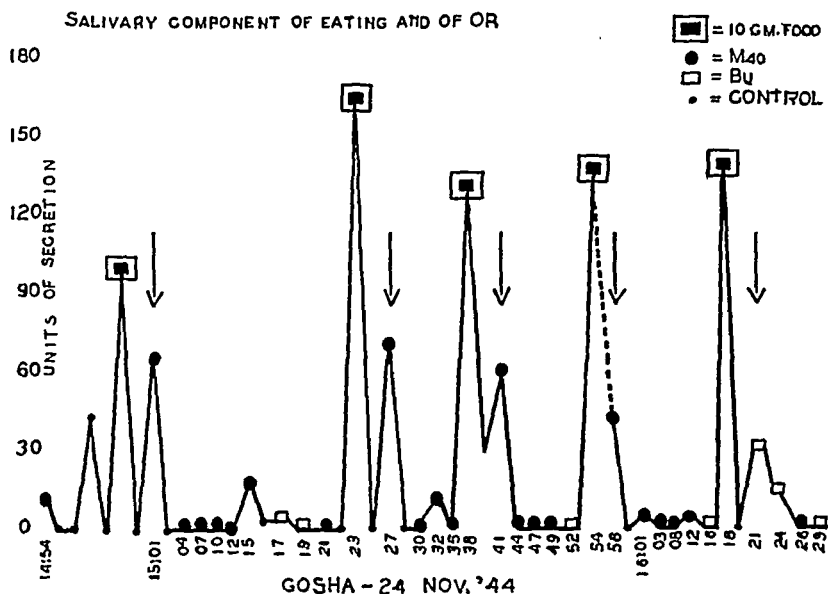


FIG. 1. SHOWING THE EFFECT OF FEEDING ON THE SALIVARY COMPONENT OF THE OR

Note increased salivation at the arrows pointing to the first neutral stimulus used after the feeding.

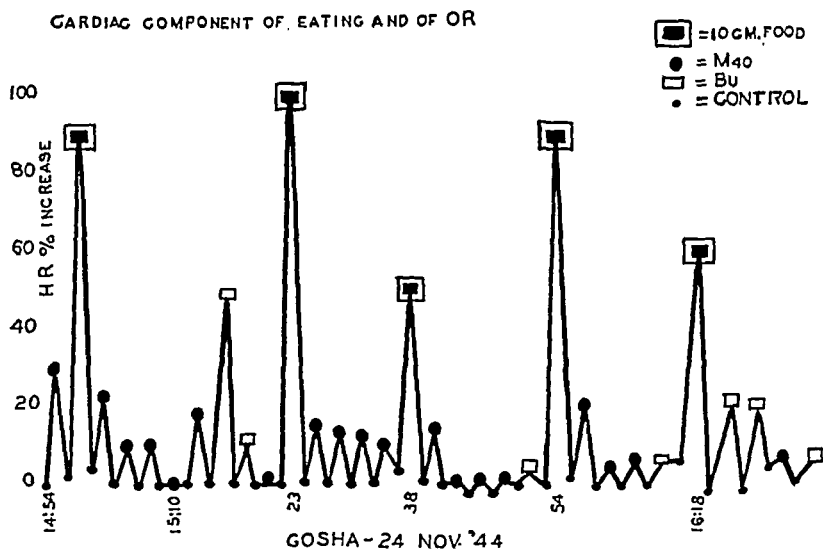


FIG. 1A. HEART RATE DURING EATING 10 GMS. FOOD AND DURING 3 SECOND ACTION OF NEUTRAL STIMULUS. Cf. WITH FIG. 1

Note the decrease of the cardiac OR on successive repetitions of the neutral stimulus.

are reported below in connection with the cardiac component of the OR.

III. Respiratory Component of the OR. A respiratory conditional reflex has been noted by many authors (Pavlov, Kellogg, Liddell, Gantt et al.). There is also a respiratory³ component of the OR, which is seen in Fig. 2. The respiratory component is less well marked, less abrupt than the cardiac component of this reaction, similar to

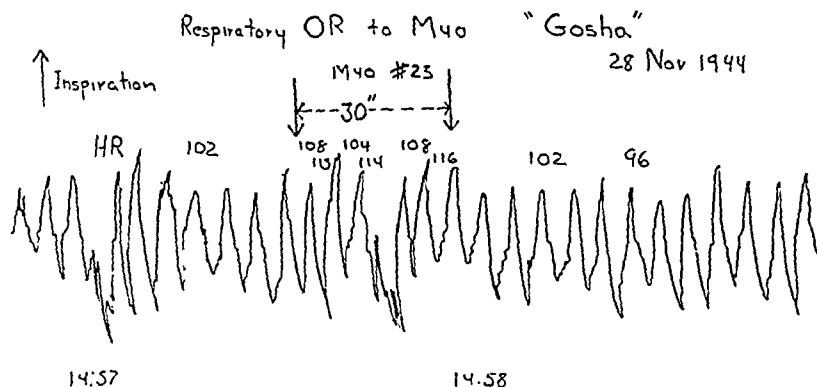


FIG. 2. RESPIRATORY OR TO NEUTRAL METRONOME (M40)

The heart rates are written in figures before, during and after the action of M40.

the difference between respiratory and cardiac components of an emotional state such as eating (Fig. 3).

In Fig. 4 we see the dropping out of the OR on repetition of the stimulus, in both respiratory and cardiac components. The respiratory movements are more readily observed and recorded than are the skeletal muscular movements but are not nearly so sensitive as the heart rates.

IV. Cardiac Component of the OR. We have found that change in heart rate is the most regular component of the OR. This was not our expectation nor original object of study in performing these experiments. Studying heart rate change in connection with the con-

³ We deal here only with the *motor* component of the respiratory reflex, i.e., the movement of the external respiratory muscles. Obviously there are other respiratory components demanding investigation, such as the gaseous exchange.

ditioning process, we had found it necessary to investigate cardiac reactions to new stimuli or sudden changes in environment as a control study for other projects, but our experience has thrown the whole matter into unexpected perspective.

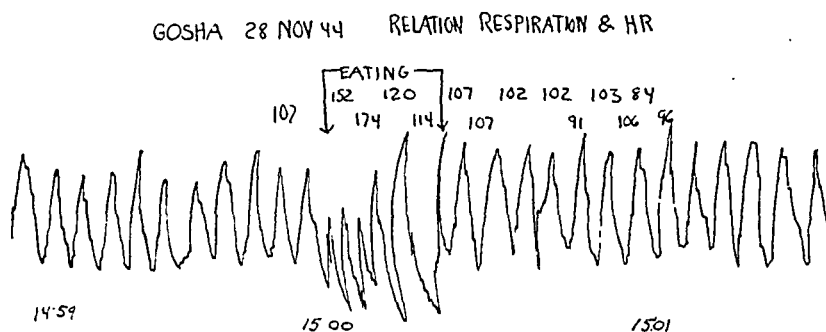


FIG. 3. RESPIRATORY AND CARDIAC CHANGES BEFORE, DURING, AND AFTER EATING 10 GMS. OF FOOD

The HRs are written in the appropriate places on the chart

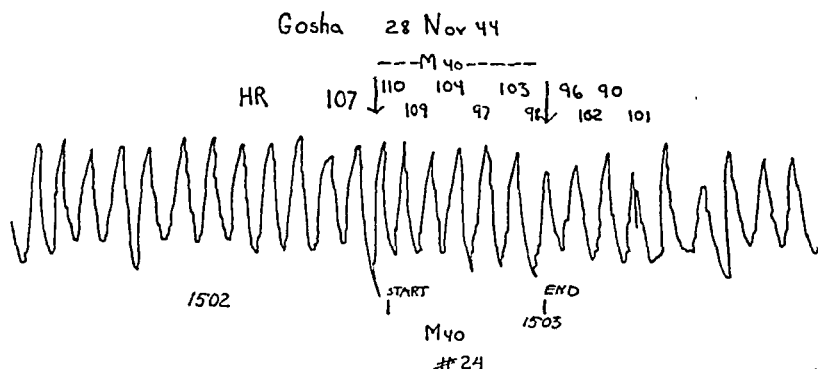


FIG. 4. SHOWING DISAPPEARANCE OF THE OR ON REPETITION

Cf. respiratory and cardiac reactions to M40 given for the 24th time, to M40 in Fig. 2 given for 23rd time five minutes previously.

In each dog studied in this series, changes in heart rate marked the occurrence of an OR, and reflected the course of its extinction, persistence, or recurrence. Fig. 5 and Table I illustrate the heart changes in one dog (Gosha) to three different new stimuli. This animal after

being accustomed to the experimental camera and eating from the foodbox⁴ was stimulated for 10 seconds with a metronome of forty beats per minute (M40) and with the sound of air bubbling through water (Bu). Neither of these stimuli were followed by food. The progressive decrease in cardiac reaction to the new neutral stimulus is seen as the stimulus is repeated (Table I). After thirty repetitions

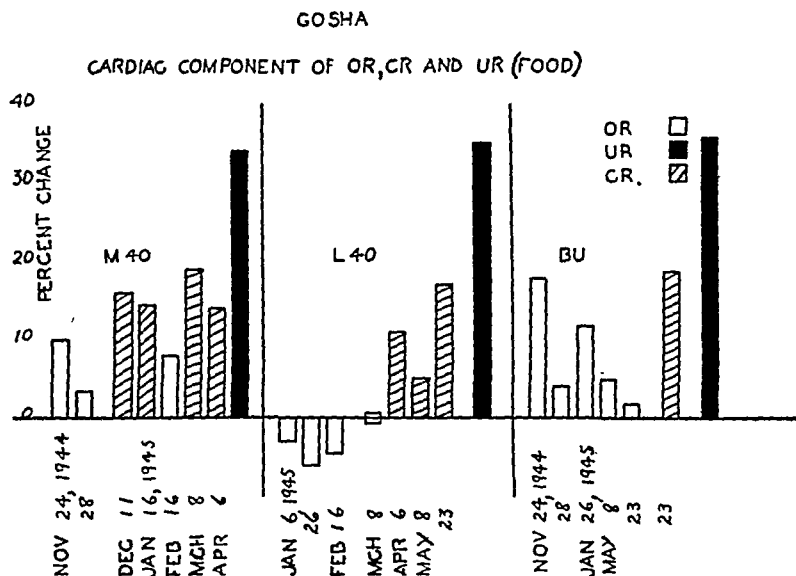


FIG. 5. CF. OF THE CARDIAC COMPONENTS OF THE OR, THE CR TO AUDITORY (M40 AND BU) AND VISUAL (L40) SIGNALS, AND TO UR, (EATING 10 GMS. FOOD)

The ordinates represent per cent changes in the heart rate from a base line of 100% control. The ordinates are for dates as marked.

of the stimulus (M40), during which the heart rate change decreased from 10% to less than 2%, M40 was then followed by two biscuits, resulting in a 72% increase in heart rate during the first 5" of eating

⁴ The practise of accustoming the animal to the unconditional stimulus alone (in this case food) before the studies of responses to neutral stimuli were made was later discontinued. For, if the food reaction (in this case) has been excited by the experimental environment (camera) *per se*, any new stimulus may release that excitement in the form of a simulated conditional salivary reflex.

(Table II). During a period thereafter when M40 was consistently employed and reinforced as a conditional food stimulus, it regularly

TABLE II
Gosha, 28 November 1944, Cardiac Rates

Symbols used are the same as in Table I with following additions. The figures in () indicate that during this reading a small non-specific auditory stimulus was given—a click of a switch. In the second part of the Table the formerly neutral stimulus (M40) is reinforced, after it has acted for 30", with 10 gms. of food. It is to be noted in this Table that the cardiac OR has nearly disappeared owing to repetition of the stimulus and that a cardiac cr is beginning to be formed.

TIME	STIM.	NO. REF.	CONTROL	OR						US (10 gm. Fd.)						INTERVAL						AV. INTERVAL	
				0° 30°						0° 30°						0° 30°							
14:55	M40	23	92	96	93	91	114	96	106	154	163	115	114	95	95	90	94	89	90	—	—	91	
15:00	Fd.		92													92	90	91	94	84	96	91	
15:03	M40	24	97	103	102	91	91	91	89							86	90	90	91	86	86	89	
15:06	M40	25	90	97	98	95	84	85	91	146	(145)	95	89	73	79	96*	88	98	89	91	88	82	89
15:08	M40	26	93	86	101	84	90	92	94							90*	80	88	88	86	88	85	86
15:11	M40	27	86	82	88	82	91	100	85							81	89	92	104	114	77	89	
15:14	Fd.		83							146	(145)	95	89	73	79	95	78	72*				89	
15:17	M40	28	81	86	77	77	66	72	61							84	88	80	66	79	79	78	
15:20	M40	29	74	67	79	82	80	92	95							71	86	79	70*			73	
15:23	Bu	8	73	60	74	70	66	74	76	79	88	66	74	64	80	75							
15:25	Bu	9	74	77	64	66	74	72	67	63	82	60	84	79	77	74							
15:28	M40	30	71	73	89	77	84	91	84	68	76	62	73	73	83	73							
Av.	M40		86	86	91	85	88	90	88	66	73	78	62	77	—	71							
Av.	Bu		74	69	69	68	70	73	72	150	154	106	102	84	87	79	85	80	83	83	83	82	
Conditional Stimulus																							
15:31	M40	31	76	72	64	77	76	61	(83)	(125)	114	91	82	73	76	70	84	92	—	—	—	82	
15:37	M40	32	75	84	84	—	—	—	73							(85)	72	72	68	64	—	72	
15:41	M40	33	78	88	104	96	84	82	89							136	142	110	100				
15:45	M40	34	86	85	85	—	—	—	—	134	135	111	102	90									
15:48	M40	35	86	80	88	—	—	—	—	126	116	91	86										
15:53	M40	36	95	96	102	—	—	—	—							92	88	(89)	(89)	84	88		
																90	98	102	108	91	109*		
																79	88*				93		
Av.			83	84	88	87	80	72	81	130	127	101	93	82	76	82	81	84	79	74	88	81	

* Readings in this line are beyond the 30" period.

elicited an OR with cardiac accelerations of about 15%. During this period a light blinking forty times per minute (L40) was presented as a new stimulus for ten seconds on certain days (results shown in Fig.

5), but it did not increase the heart rate, although it produced a very slight motor OR. Indeed the response to L40 was accompanied with a slight decrease in heart rate. After thirty repetitions of L40, it was then followed by two biscuits, exactly as with M40. Thereafter when L40 was consistently used as a conditional food stimulus it regularly elicited cardiac accelerations of about 10%. While L40 readily became a conditional stimulus for food, it was not as strong a conditional food stimulus as M40, nor did it have as much effect upon heart rate, after this initial use as a food signal. That visual signals do not produce as strong a cr for the dog as the auditory, even when the same unconditional stimulus is employed, was first noted in Pavlov's laboratory (1).

When L40 had been firmly established as a conditional food stimulus, the new auditory stimulus of air bubbling through water (Bu) was introduced, and repeated. The regular OR sequence was observed, a fairly marked initial reaction, diminishing on repetition of the stimulus. After nineteen repetitions without food, Bu was followed by two biscuits. Thereafter, as a conditional food stimulus, Bu elicited marked cardiac accelerations, about 18%, as shown in Fig. 5.

The effect on the heart rate of a lapse of time in restoring an extinguished OR is seen in Fig. 5 with Bu. On the 28th November 1944 the cardiac component of the OR had practically been extinguished. After two months without using this stimulus it was again used (on 26th January 1945) and the HR response was nearly as large as it was when first used on 24th November 1944.

The results of somewhat similar experiments on Connie, using the stimuli Bu and L40 are shown in Fig. 8. In this dog the HR response to new stimuli decreased sharply, rather than gradually, after the first time given on each trial day.

With two dogs (Connie and Harry) the cardiac response to the 10" sounding of a buzzer was measured forty times. The intensity of the OR was markedly different in the two dogs, Harry showing much less reaction than Connie, but both showing the usual diminution of response as the novelty diminished. The buzzer was then made a conditional stimulus for artificial sexual excitation produced by peripheral stimulation. The increase in cardiac response after the buzzer had become a sexual conditional stimulus is shown diagrammatically

in Fig. 5⁵ (Harry). Connie on the contrary showed a slowing of heart rate to the buzzer when it was made a conditional sexual stimulus. These differences in reaction may be dependent on the temperament of the dog. Harry, who showed definite cardiac acceleration to sexual conditional stimuli, had extremely hypoactive ORs. This dog is a lethargic, slow moving animal of the extreme phlegmatic type, difficult to excite with any stimulus.⁶

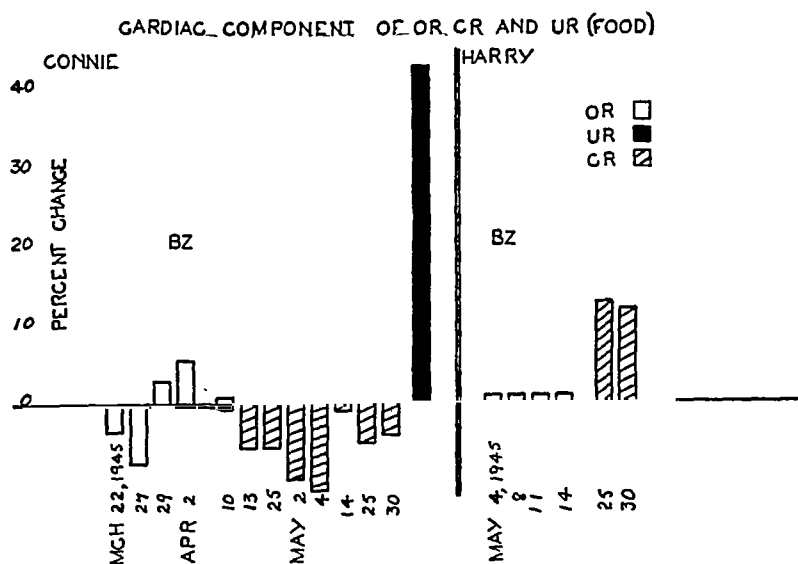


FIG. 6. COMPARISON OF CARDIAC ORs TO NEUTRAL SIGNALS WITH 1) CARDIAC CRs TO THE SAME SIGNALS AFTER BECOMING CONDITIONAL STIMULI FOR SEXUAL EXCITATION AND WITH 2) UNCONDITIONAL SEXUAL STIMULATION

The cardiac responses of two other animals (Tom and Clare) to a new stimulus are shown in Fig. 7. These dogs were accustomed to the camera, then repeatedly stimulated for 3 seconds with tones of

⁵ This measurement of the cardiac component of the conditional sexual excitation is the first clear index which we have seen of artificial sexual conditioning based on peripheral stimulation.

⁶ In other experiments, persistence and hyperintensity of the OR appeared to be a sensitive indicator of general hyper-reactivity.

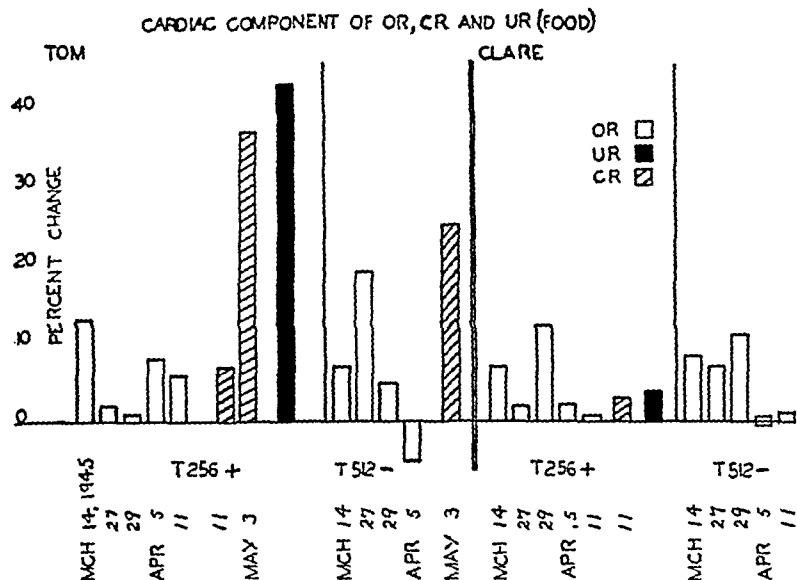


FIG. 7. COMPARISON OF CARDIAC COMPONENTS OF ORs TO NEUTRAL SIGNALS (TONE) WITH 1) THE SAME SIGNALS USED AS EXCITATORY (T256) AND INHIBITORY (T512) CRS AND WITH 2) THE EATING OF 10 GMS. OF FOOD (UR)

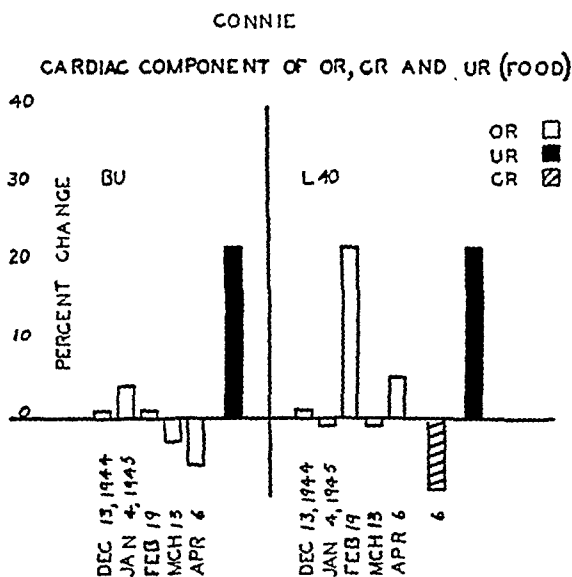


FIG. 8. CARDIAC COMPONENTS TO AUDITORY (BU) AND TO VISUAL (L40) NEUTRAL STIMULI COMPARED WITH THE CARDIAC COMPONENT OF THE CR AND UR TO FOOD

256 and 512 vibrations per second. In both cases the OR to the new stimulus diminished with repetition, altho in a varying degree and pattern in each animal. After approximately thirty repetitions of each tone, T256 was followed by a light electric shock to the foot, while T512 was given as before without reinforcement. Generalization of excitation extending to the conditional stimulus (T512) before differentiation is also apparent. In the dog Tom a marked OR was thereafter elicited by T256. The motor component of the OR diminished as usual on repetition, but the heart rate response continued to be large, as shown in the experiment of May 3 after forty-five combinations of T256 with shock.

The dog Clare went through an identical control period and conditioning process, with results shown in Fig. 7. Altho a slight conditioning occurred on March 11, this dog had to be discarded soon after, as she began struggling violently and continuously in the camera and could not be used for experimental work.

OR in Decorticated Dogs. Pavlov had previously noted the existence of the OR in decorticated animals, and its failure to be extinguished on repetition of the stimulus. Altho we did not have any completely decorticated animals in this series; two of our dogs (Checkers and Crazy) had been completely decorticated on one side, and on the other side the gyrus fornicatus on the mesial surface had been extirpated.⁷

These two dogs gave ORs which were not characteristically different in either the motor or the cardiac components from those of normal animals. In Checkers the cardiac OR to a tone of 256 vibrations acting for 5 seconds was characterized by an increase in heart rate from 120 to 140 (average of first eight readings). In Crazy the heart rate decreased from 95 to 86 on the first day the tone was tried (average of 22 repetitions of the tone on 5 November 1946), and from 92 to 89 on the 12 December 1946 (average of 20 repetitions of the tone). This animal shows less cardiac change to subsequent repetitions than he does to the first repetitions, as would be expected in a normal animal.

Startle Reflex. Altho the role of the startle reflex in the OR has not been investigated, there is nevertheless evidence of a relationship. Hunt says:

⁷ These dogs, which had been prepared for other experiments, are to be reported in detail with Dr. Clinton Woolsey in further studies on the relation of cortex to cardiac reactions.

"It would also be possible to interpret the startle pattern as an orienting reflex in itself. Witness the way that in animals the generalized flexion seems to place the animal in a posture particularly suitable for the initiation of flight. I suppose, too, that when Kurt Goldstein speaks of startle as a catastrophic response, he is also in one way thinking of it as an orienting reflex.

"In connection with our studies in the startle pattern, we did find in the course of extinguishing it that it was subject to disinhibition by other stimuli."⁸

In spite of the fact that the startle reflex may play a role in the OR, there are marked differences. The former is a sharp, brief, non-directed movement, often appearing to the naked eye as a jerk, completed in 0.3 to 1.5 seconds. In contrast to the OR the startle reflex as described by Hunt and Landis has a definite pattern "beginning with the eye blink and passing downward over the body. The response is too rapid for the eye, coming and going in less than $\frac{1}{2}$ second . . . the initial pattern was followed by less rapid secondary responses, viz., orientation to the position of the stimulus" (3). The movement in the OR, however, is specifically directed toward the source of the stimulus—an alert, forward, steady, focusing—aptly described by Pavlov as the "what-is-that" reflex. Furthermore the question of cardiac changes accompanying the startle reflex has not been definitely settled. Professor Hunt writes (to WHG) on 7 January 1947: "It was my opinion that while the cardiac reaction did not show uniformities of response, a more subtle analysis in the future might reveal such uniformities." There is an indication from the work of Landis and Slight (4) that the pulse rate increases but Landis and Forbes (5) state it is influenced by the phase of the cardiac cycle during which the stimulation takes place. Since they were measuring reactions that occurred in less than a second, they could not be certain that HR changes were elements of the primary startle pattern.

Some indication of the difference in the cardiac rates *following* a startle reflex and those accompanying the OR are shown in Fig. 9: there is a sudden and marked rise in HR to a stimulus (click of a switch) which elicited at 2 a quick undirected jerk of the dog (startle reflex) without further change, contrasted with the same stimulus which for some reason elicited an OR at 1 and 3.

Whitehorn found in the human being to a "startling stimulus" "only a slight or questionable emotional change and the heart record

⁸ Personal letter to one of the authors (W. H. G.) 20 January, 1947.

showed little if any deviation from its previous character" (6). His results in patients are comparable to the small heart rate changes with the OR which we found in some dogs, eg. Harry, who later gave a strong OR and also became neurotic.

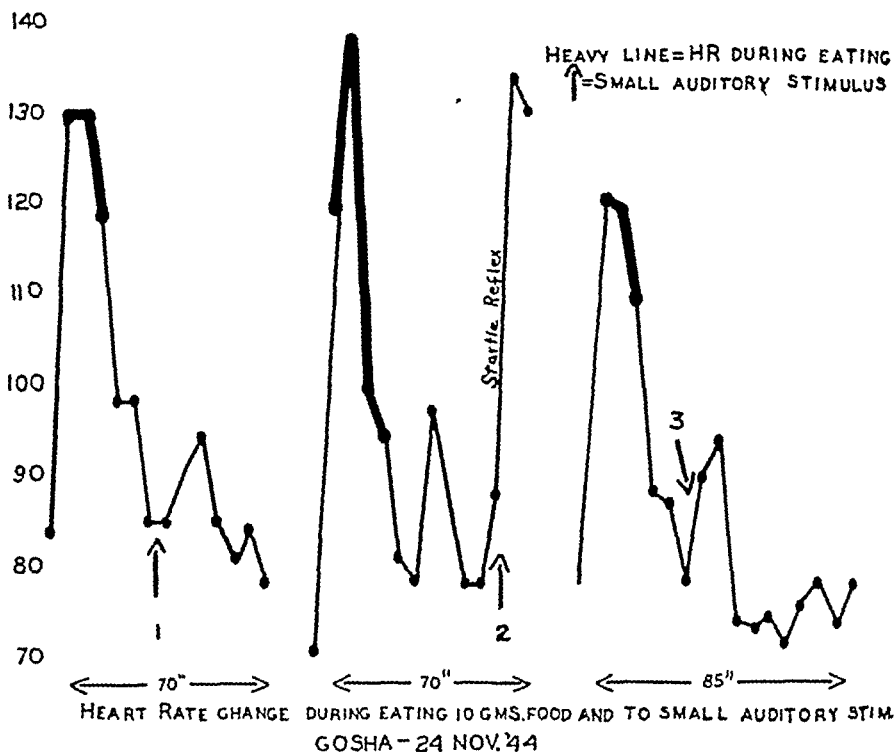


FIG. 9. COMPARISON OF CARDIAC RATES BEFORE, DURING, AND AFTER EATING 10 GMS. OF FOOD WITH A NEUTRAL STIMULUS INTRODUCED AT 1, 2, & 3

Note the difference in reaction to the neutral stimulus depending upon "the state of the animal."

OR AND TEMPERAMENT

Both the motor and cardiac components of the OR as seen in the figs. vary from dog to dog as well as with different stimuli. In general a dog that gives a strong OR to one stimulus will give a strong OR to

all stimuli. The most phlegmatic dog Harry—a very slow moving lethargic type hound—did not give an OR judged by heart rate tho he did in movement to two tones and a buzzer. On the other hand most dogs considered excitable in their ordinary behavior show a definite OR both motor and cardiac. The question of temperament is a complex one, and a satisfactory means of studying temperaments has not been seen in this laboratory.

COMPARISON OF CARDIAC AND MOTOR COMPONENTS OF THE ORIENTING REFLEX

Tables I and II show the parallel readings of the HR and the observed motor components of the OR. In Table I the HRs during which there was a motor OR observed, i.e., a turning of the dog or other directed movement, are in *italics*; with stimulus number 1 for example, there is a motor OR during the whole 30 seconds but the HR fluctuates from 106 at the beginning to a low point of 79 between 15 and 20 seconds.⁹ An examination of these records show that the HR may go up without a movement being made and that vice versa a movement may continue without increase of HR; there is not always a temporal parallelism between the cardiac and the motor component. In general the cardiac component appears earlier than the motor. Thus with stimulus number 3 the HR goes up from 83 to 94 within 5 seconds while there is no movement made until 8 seconds, and tho the movement continued unchanged until the end of the metronome the HR drops from a peak of 114 at 10" to 73 at 25".¹⁰

In general, however, one finds a high correlation between the observation of the motor components of the OR and the heart rates recorded during the time of these movements. We find in the dog Gosha those movements marked "strong" accompanied by heart rate of 91 (median of eight 5 second readings); movements marked "medium intensity" by HR of 86 (median of sixteen 5 second readings);

⁹ Also those HRs coinciding with the eating movements (chewing, swallowing) are in bold face in the column "Food," and the HRs during the act of licking the food box (without food) are starred.

¹⁰ Both Whitehorn (6) and Hoffman (unpublished data from this laboratory) have shown that heart rate changes more often precede than accompany simple changes in position where there is no apparent motivation.

movements marked "weak" by HR of 80 (median of twenty-four 5 second readings). (The observed movements were marked without knowledge of the heart rates). There is thus a close parallel between the intensity of the motor and cardiac components in a given animal.

RELATIONSHIPS BETWEEN OR, CRS AND OTHER FACTORS

How one and the same stimulus may produce varying effects at different times depending on some unknown factor, most probably the *state of the animal*,¹¹ is seen in Fig. 9 when at one moment a slight clicking noise produces an OR and a few minutes later in the same animal a startle reflex with markedly higher HR. It appears that the state of alertness of the animal, the mood or attitude, the previous stimuli, the degree of hunger and a number of such factors may determine whether a new stimulus will elicit an OR or some other type of response.

The OR to a new stimulus modifies the other responses of a subject depending upon temporal relations determining the state of the organism. If the new stimulus elicits an OR during the early part of a delayed cr it inhibits the inhibition (disinhibition) resulting in a prompt appearance of the cr which is normally inhibited during the first stage of the delayed cr. If the new stimulus elicits an OR during the second stage of a delayed cr, i.e., when the cr is appearing, the OR inhibits the activity, resulting in a complete inhibitory state (7).

In the previous pages are numerous observations on the relationships between salivary reactions and the OR. These facts are of interest not only in connection with the OR but as evidence of the importance of the state of the organism for determining what effect a given stimulus will have.

DISCUSSION

The cardiac component of the OR is of interest therefore for both a description of the OR and in the detailed study of the cardiac crs. Previously the OR (reaction of the animal to a new stimulus or change of the environment) could not be evaluated because of the crude method of measurement—the casual observation of ordinary move-

¹¹ This term is used to cover factors *probably* in the animal, not always known, when the external environment is kept apparently constant.

ments. The study of the cardiac component provides not only a quantitative objective measure but a more complete picture of what is happening to the organism. Although the cardiac is probably the most reliable index, a consideration of all the components (motor, salivary, respiratory, cardiac) is not to be minimized.

The comparison of the various components of the OR present a somewhat varying picture depending upon what measures we use: if we adhered to any one component we would come to slightly differing conclusions. Synthesizing the components we arrive at a point similar to what obtains with a repeating decimal: the more measures we take the nearer we come to the truth and though we can approach the real answer we can never arrive at it completely. An increase in the number of components that are objectively recorded always brings us closer and closer to the whole picture and even though our synthesis can never correspond exactly to the thing represented it may, provided we are careful, serve our practical purposes.

In animals subjected to severe nervous strain in the laboratory we have observed the reappearance of an OR which had been inhibited, or a marked increase in its intensity, if only partially inhibited, and in nervous patients we have noted exaggerated ORs. Such observations have led us to suspect that the persistence of a strong OR may be an indication of susceptibility to breakdown, or its reappearance may be a symptom of approaching acute nervous disturbance, as well as a pattern of uninhibited reactivity. It is usually exaggerated in anxiety states. In World War II, in soldiers returned from combat, with acute neurotic breakdown, but not in non-neurotic soldiers returning from combat, it was frequently noted that there were exaggerated responses to neutral stimuli—startle, tremor and somatic complaints, alteration of heart rates and of respiratory patterns.¹² Perhaps these reactions are components or phases of an orienting reflex.

The reappearance of the OR under nervous stress may represent a disinhibition of cortical inhibition, releasing the subcortical reflex (OR). It may be a result of the general weakening of cortical processes,

¹² The valuable observations made by Victor H. Rosen and W. G. Reese on such soldiers are the basis of the above statement. These will be published in detail. I am indebted to Dr. Rosen for the account.

the most labile of which are the inhibitory. Thus we see the ORs becoming prominent during certain stages of the action of alcohol (8, 9), or of narcotics. Wolff and Gantt (10) have noted the appearance of the formerly inhibited ORs in both the incipient and emerging stages of anesthesia just at the time the crs were disappearing or as they began to reappear.

From the marked increase in HR to new and unaccustomed stimuli (auditory, visual) or to simply a change of environment it is apparent how a normal heart can be stimulated and a failing heart possibly placed under a burden by any quick changes of the environment, and by the law of extinction of the OR through repetition how the city dweller remains less stimulated by the metropolitan routine than the rural visitor. This brings up such questions as what constitutes healthy and beneficial and what harmful stimulation for the normal as well as for the pathological heart?

SUMMARY

A stimulus which had no previous known association for the dog produced in most animals an "orientation" toward the stimulus (turning, pricking ears, etc.). This orienting reflex was characterized by directed muscular movements, and by respiratory, salivary, and cardiac reactions, which were present even in dogs deprived of most of the cortex. The cardiac is the most definite, the most constant and the most easily evaluated of all these reactions. The OR disappears in most individuals (both dog and human) after several or more repetitions of the neutral stimulus; its persistence, a sign of hyperreactivity, is seen in both animals and patients.

We desire to thank Dr. Whitehorn for his suggestions, and for his generous help in the organization of the data of this paper.

REFERENCES

1. PAVLOV, I. P.: Lectures on Conditioned Reflexes. (Tr. Gantt) International Publishers, N. Y., 1928, vol. I, p. 134.
2. GANTT, W. H.: Experimental Basis for Neurotic Behavior. Hoeber and Co., N. Y., 1944.
3. LANDIS, C., AND HUNT, W. A.: The Startle Pattern. Farrar & Rinehart, Inc., N. Y., 1939.
4. LANDIS, C., AND SLIGHT, D.: Studies of Emotional Reactions: VI. Cardiac Responses. J. Gen. Psychol., 1929, 2: 413-20.

5. LANDIS, C., AND FORBES, T. W.: The Relation of the Startle Reactions to the Cardiac Cycle. *Psychiat. Quart.*, 1934, 8: 235-42.
6. WHITEHORN, J. C., KAUFMAN, M. R., AND THOMAS, J. M.: Heart Rate in Relation to Emotional Disturbances. *Arch. Neurol. and Psychiat.*, April, 1935, 33: 712-731.
7. PAVLOV, I. P.: Conditioned Reflexes. (Tr. Anrep) London, 1927, p. 98.
8. GANTT, W. H.: Effect of Alcohol on Cortical and Subcortical Activity Measured by the Conditioned Reflex. *Bull. Johns Hopkins Hosp.*, 1935, 56: no. 2, 61-83.
9. FINKELSTEIN, N., ALPERN, B., AND GANTT, W. H.: Amphetamine (Benzedrine) Sulfate upon Higher Nervous Activity Compared with Alcohol. *Bull. Johns Hopkins Hosp.*, 1945, 76: no. 2, 61-74.
10. WOLFF, H. G., AND GANTT, W. H.: Caffeine Sodibenzoate, Sodium Iso-Amylethyl Barbiturate, Sodium Bromide and Chloral Hydrate. *Arch. Neurol. and Psychiat.*, 1935, 33: 1030-1057.

NEURINOMAS OF THE CEREBELLOPONTILE RECESS

A CLINICAL STUDY OF ONE HUNDRED AND SIXTY CASES INCLUDING OPERATIVE MORTALITY AND END RESULTS

ANTONIO GONZALEZ REVILLA, M.D.

From the Department of Surgery (Neurosurgery), The Johns Hopkins Hospital

Neurinomas of the cerebellopontile recess have been the subject of magnificent monographs (5, 18) in which the so-called syndrome of the cerebellopontile angle has been elucidated. In the course of clinical studies of patients with proven neurinomas, we have found such wide variations in the incidence, chronology of symptoms and signs that we deemed it worthwhile to review all the cases operated on at the Johns Hopkins Hospital in a period of twenty years. In a subsequent communication we shall analyze all other tumors seen in this location in the same period in order to clarify the differential diagnosis.

From 1926 to 1945 a total of one hundred and sixty cases of neurinomas of the cerebellopontile recess have been found at operation. The operation was performed in almost every instance by Dr. Walter E. Dandy.

The accompanying table will give the relative incidence of these tumors in regard to the cranial nerves affected as well as their solitary or multiple locations.

UNILATERAL ACOUSTIC NEURINOMAS

It is common knowledge that neurinomas occurring in the posterior fossa originate predominantly from the VIIIth N., and in our series there were 145 (90 per cent).

Etiology: The relationship of trauma and infection in precipitating symptoms have been emphasized sporadically in the literature. Twenty-one cases (13.8 per cent) gave a history of infection or trauma coincidental to the initiation of symptoms. In ten of them there was definite history of middle ear infection on the same side as the lesion. Three cases dated their symptoms from an attack of influenza and one during the course of typhoid fever. Five gave a history of trauma on the affected side of the head with transient loss of consciousness and two related their impairment of hearing to pistol shooting.

Many arguments have been put forward that neurinomas at the angle are a manifestation of von Recklinghausen's disease. However, one marvels at the low incidence of peripheral lesions in this series, only three such cases occurring in this group. These shall be discussed separately due to some important clinical differences.

The hereditary tendency of these tumors has also been mentioned, but not a single instance of these one hundred and forty-five cases was encountered in contradistinction to the bilateral tumors where this tendency appears to be quite definite.

Incidence: 1. Sex: Ninety-one females (62.8 per cent) and fifty-four males (37.2 per cent) were affected. Why females should be more

TABLE 1
Neurinomas of the cerebellopontile angle

Unilateral acoustic neurinomas.....	145
Bilateral acoustic neurinomas.....	6
Unilateral acoustic neurinomas and von Recklinghausen's neurofibromatosis.....	3
Neurinomas of the Vth N.....	3
Neurinomas of the Xth N.....	2
Neurinomas of the XIth N.....	1
Total.....	160

predisposed to these neoplasms is not apparent, but this is also true in the meningiomas and in many of the gliomas in this location. These figures correspond closely with those given by Cushing (5) and Olivecrona (24), but not by Henschen (18) who found no definite predisposition.

2. Location: There was no significant predilection of sides. 46.9 per cent were present on the right and 53.1 per cent on the left.

3. Age: The average age on admission was 44.1 years, the youngest 19 and the oldest 69. However, the average age at the onset of symptoms was much earlier; e.g., 39.6 years, the youngest 12 and the oldest 69. Consequently, an average of 4.5 years has elapsed between the onset of symptoms and the time of admission to the hospital, the shortest being 6 weeks and the longest 20 years. These figures are a little higher than Cushing's (5) who gives 38.1 years as the average age on admission and 34.1 years as the age of onset (30 cases). These

figures should be remembered in discussing other tumors at the angle as they may be of importance with respect to differential diagnosis.

Chronology of Symptoms: Since the publication of Cushing's classical dissertation on acoustic tumors emphasis has been placed repeatedly on the chronology of symptoms postulated by him, namely: 1. Auditory and labyrinthine manifestations; 2. the occipito frontal pains with suboccipital discomfort; 3. the incoordination and instability of cerebellar origin; 4. the evidences of involvement of adjacent cranial nerves; 5. the indications of increased intracranial pressure with a choked disk and its consequences; 6. dysarthria, dysphagia and finally so-called cerebellar crises and respiratory difficulties. Nielsen (24), in reviewing Olivecrona's 130 cases, points out that most of his cases followed this pattern and Olsen and Horrax (25) in their series of 52 cases found out that this chronologic order of symptoms was almost infallible. They concluded that if the complex of symptoms was not typical some other type of tumor was likely to be present.

In a careful review of our cases we find a great variance in the chronologic order and no definite pattern can be discovered. Only 45 cases (31 per cent) followed the chronology postulated by Cushing. In 30 per cent the Vth N. was affected shortly after the onset of auditory and labyrinthine disturbances. Incoordination and other manifestations of involvement of the cerebellar pathways followed symptoms referable to the VIIIth N. in 20.7 per cent. Headaches, occipital pains or suboccipital discomforts preceded even the auditory manifestations in 12.4 per cent and in 6 per cent no definite pattern was followed. This great variation may be easily explained by the relative vicinity of the anatomical structures at the cerebellopontile recess, by variation in the degree and direction of the growth and by individual anatomical differences.

Subjective Disturbances: Auditory and labyrinthine: Subjective evidence of either auditory or labyrinthine disturbances was present in every case. History of diminution of hearing was elicited in all but one, in spite of the fact that there was no objective evidence of hearing loss in five, as we shall see later.

Tinnitus was present in 62.3 per cent, being bilateral in nine and contralateral in three. It usually appeared simultaneously with the subjective impairment of hearing, less frequently followed it and

rarely preceded it. In only one case tinnitus was present without appreciable loss of hearing.

Dizziness was elicited in 40.8 per cent, far less frequent than tinnitus. In half of the cases it was described as true rotary vertigo and in the rest as a sensation of subjective dizziness or loss of balance. Dizziness usually followed impairment of hearing, occurring less frequently before or simultaneously.

Auditory and labyrinthine disturbances represented the initial symptom in 68.6 per cent of the cases, in four of which they represented the only symptoms present on admission and were operated on subsequently with the preoperative diagnosis of Ménière's disease.

Cerebellar: Cerebellar symptoms were next in order of frequency in this series. They occurred in 86.2 per cent and usually affected the upper and lower extremities on the same side as the lesion. The usual complaint was either unsteadiness in walking, staggering or clumsiness of one extremity. Three cases gave a history of bilateral cerebellar involvement, one of disturbances on the contralateral side and in three incoordination of the ipsilateral arm alone. In 3.1 per cent cerebellar disturbances were the initial symptom. The average duration of cerebellar symptoms was 8 months and the average time interval between the acoustic disturbances and these manifestations was 3 years.

Headaches: They were slightly less frequent than the cerebellar disturbances, occurring in 68.2 per cent. They represented the initial symptom in 12.4 per cent. The headaches were mostly localized in the occipital region, although at times they were described as suboccipital discomfort or pain behind the ear. In other instances they tended to radiate to the frontal region on the homolateral side; this type of radiation being present in half the cases. In eighteen cases the headaches were generalized and in nineteen cases they were only bifrontal. Vertical headaches or a sensation of fullness in the head were experienced in four cases. Curiously enough, in only sixteen cases the headaches were increased by coughing, sneezing and straining, contrary to the experience of other observers.

The average duration was 1.5 years and the interval between the onset of headache and the auditory disturbances was 3.3 years.

The relationship between headaches and pressure upon the trigeminal

nerve has been mentioned by others (25), and we thought it interesting to try to correlate these symptoms. In one hundred and twenty-one cases (83.5 per cent) headaches and trigeminal symptoms existed together or separately. Headaches preceded Vth N. symptoms in thirty-one cases with an average interval of 1.9 years. On the other hand, Vth N. symptoms preceded headaches in twenty cases with an average interval of 2.2 years. Headaches were present without trigeminal manifestations in forty patients and conversely trigeminal symptoms occurred without headaches in twenty-two. Both symptoms appeared simultaneously in only eight cases. This correlation of figures would tend to disprove the previous assertion, but one is struck immediately with the similarity of the duration of headaches and trigeminal symptoms, e.g., 1.5 and 1.6 years, respectively, as well as the time interval between these symptoms and the acoustic disturbances, 3.3 years in each instance. Then these figures would tend to show that pressure of the neoplasm on the Vth. N. might be manifested by headaches or by disturbances in the sensory distribution of this nerve on the face, although one cannot escape the fact that acoustic tumor headaches may also be produced by pressure on the neighboring meninges, vessels and possibly on the IXth N.

Trigeminal: Symptoms referable to involvement of the trigeminal nerve were found in 56.5 per cent. Numbness of the face was the predominant manifestation occurring in sixty-three cases: it was mostly on the same side as the lesion, being contralateral in one and bilateral in another one. Tingling was present in five and burning in one.

Typical tic douloureux, with or without numbness, was present in sixteen cases, contrary to the experience of Cushing who did not find a single instance in his series. However, there are scattered reports in the literature confirming this finding, Dandy's (7, 8, 9) observations being outstanding. The pain was almost invariably unilateral; in only one instance it appeared opposite the side of the lesion and at operation in this case it was found that the tumor extended beneath the brain stem to the opposite side. Of these cases, eleven were admitted with the chief complaint of tic douloureux and with this diagnosis they were operated on. At operation through the unilateral cerebellar approach typical neurinomas were found at the angle. These cases

have been summarized by us in a previous communication (15) and in analyzing them we found that there was unilateral impairment of hearing in ten, which was not considered significant at the time, if the age group between 50 and 70 years was taken into consideration.

Subjective involvement of the motor root was elicited in two.

The average duration of trigeminal symptoms was 1.6 years and the time interval from the auditory symptoms was 3.3 years. The similarity of these figures with the ones found in headaches has already been remarked upon.

Symptoms referable to other cranial nerves: There was no subjective anosmia in any of the cases. Disturbances of vision will be discussed subsequently under symptoms produced by increased intracranial pressure. Subjective manifestations of VIth N. involvement were elicited in 17.7 per cent (25 cases) although objectively could be corroborated in only twenty-one cases. The average duration of diplopia was 1 year and the interval from the onset of acoustic disturbances was 4.3 years, therefore occurring rather late in the course of the illness and it never preceded the VIIIth N. symptoms.

The VIIth N. was subjectively affected in 15.8 per cent. In fifteen cases there was a history of facial weakness on the same side as the lesion. Ipsilateral spasms of the facial musculature occurred in four cases and typical gustatory fits were present also in four. The duration of facial symptoms was 5.2 years and the interval from the onset of auditory disturbances was 3 years. Facial manifestations always followed symptoms referable to the VIIIth N.

Dysphagia and dysarthria were present in 16.5 per cent, with a duration of 0.5 years and an interval from the onset of acoustic symptoms of 2.5 years. They followed auditory disturbances in every instance.

The XIth and XIIth Nerves were not affected subjectively.

Symptoms due to increased intracranial pressure: It is quite difficult to determine subjectively what constitute the symptoms of intracranial hypertension. Evidence has been presented (32) that the headaches in intracranial neoplasms are predominantly due to pressure of the tumor on neighboring structures and not due directly to increased intracranial pressure. Furthermore, as explained above, we think that acoustic tumor headaches, especially, are produced by pressure of the

growth on the sensory root of the trigeminal, neighboring meninges and vessels and possibly on the IXth N. In any event, headaches in this type of tumors come relatively early, sometimes representing the initial symptoms, and in many instances they were not associated with objective evidence of increased intracranial pressure. Blurring of vision might be considered a sign of increased pressure if associated with papilledema. Papilledema, however, might be present with no subjective evidence of diminution of vision, and, furthermore, increased intracranial pressure might exist without papilledema. Nausea and vomiting are symptoms of increased intracranial pressure but might also be associated with attacks of rotary vertigo, which were not uncommon in this series. Loss of sphincteric control and loss of consciousness are late manifestations, quite rare in this group of cases and therefore not good criteria. So it is obvious that an accurate estimate of the onset of symptoms of increased intracranial pressure is hardly possible. However, we have listed as symptoms of intracranial hypertension, blurring of vision associated with papilledema on examination and nausea and vomiting not accompanied by attacks of vertigo. There were 62 cases (47.2 per cent) fulfilling these criteria. However, there were thirty-six additional cases showing papilledema on admission without subjective evidence of blurring of vision or nausea and vomiting. The average duration of symptoms was 1.1 years and the time interval from acoustic manifestations was 4.5 years.

Tonic convulsions: We have carefully avoided the use of the term "cerebellar crises" as proposed by Jackson (19) and used by other authors. Most authorities are inclined to attribute them to lesions in the brain stem, most likely in the midbrain. There were only six cases (4.1 per cent) who gave a history of tonic convulsions, all of which occurred as very late manifestations. Four of these patients recovered after the operation and two died, showing, therefore, that when this stage is reached there is still chance for recovery, contrary to the views of others.

Objective Findings: State of consciousness: On admission most of these patients were alert and cooperative. One hundred and thirty-four (92.4 per cent) showed no disturbances of consciousness. Six (4.1 per cent) were drowsy and confused and five (3.5 per cent) were comatose.

Cranial Nerves: I. Anosmia has been described by others as a common feature in cases with increased intracranial pressure. In our series, however, it was quite rare and appeared in only three cases, being bilateral in all.

II. There was no impairment of visual acuity in ninety cases (68.1 per cent). Partial diminution of vision was elicited in forty-four cases (30.3 per cent), one of which showed complete loss of central vision. Total loss of vision was present in eleven (7.6 per cent). It is interesting to notice that in one case there was a history of visual hallucinations.

The visual fields were reported as normal in all the cases with normal vision. In patients with impaired vision the fields were reported as normal in half of them, the other half showing concentric constriction or bizarre changes.

Papilledema was a common, but not a constant finding, occurring in ninety-eight cases (66.5 per cent). It was described as slight in nineteen, moderate in fifty-one and massive in twenty-eight. Retinal hemorrhages accompanied choking of the discs in nineteen cases. They were not recorded as an isolated finding. Secondary optic atrophy was present in eighteen and macular degeneration in one.

III, IV and VI. Pupillary abnormalities were quite rare. One patient showed the ipsilateral pupil to be large and fixed, and another showed both pupils to be large and fixed without ptosis or limitation of the extraocular movements. Ptosis of the eyelids was not recorded in a single instance. Paralysis of the rectus externus was less frequent than we would expect in patients with intracranial neoplasms. It was present in twenty-one cases (14.5 per cent), being ipsilateral in twelve and bilateral in nine.

V. The Vth N. was, with the exception of the VIIIth, the cranial nerve most commonly affected; in fact, it was almost a constant finding in our series. One hundred and twenty-five cases (86.2 per cent) showed some degree of sensory impairment either on the face or corneae. This figure would increase if seven cases of tic douloureux without demonstrable sensory changes are included, boosting the total to one hundred and thirty-two cases (91 per cent). The corneal reflex was either diminished or absent in one hundred and twenty-two, in fourteen of which the involvement was bilateral. Complete or partial

sensory changes in the face or tongue were elicited in ninety-three, in three the involvement was bilateral, and in one in which the corneal involvement was ipsilateral, the sensory loss was contralateral. Corneal and facial sensibility were affected simultaneously in ninety-one cases.

Involvement of the motor root was quite rare, occurring in nine cases (6.2 per cent). The temporals, masseters and pterygoids were similarly affected. In only one case was the involvement bilateral. From this rare involvement of the motor branch we may derive that these neoplasms rarely grow as far forward as to impinge on the motor root of the Vth N.

VII. As the VIIth N. is in close association with the VIIIth N. one would expect a large incidence of facial paralysis in this kind of tumor. This is not the case, however. Facial paralysis was present in seventy cases (48.3 per cent). In fifty-three cases the paralysis was incomplete, affecting mostly the lower two-thirds of the face and in many instances was confused with the central type. Typical complete Bell's palsy was quite rare, occurring in seventeen cases. In one case the facial paralysis was contralateral to the lesion and in another there was bilateral involvement.

Tests for taste, unfortunately, were not done in most of our cases so they are not included in this study. It is interesting to note, however, that in four cases there was absence of taste in the anterior two-thirds of the tongue on the affected side, without apparent facial weakness, indicating that taste fibres might be affected at times much earlier than the motor fibres.

VIII. a. Auditory: Audiograms were taken in every patient except in one who was comatose on admission. Four other comatose patients had audiograms performed elsewhere previous to admission. Complete or partial deafness was the most common sign in our series. The neurogenic type of deafness was confirmed in all affected. One hundred and thirty-nine cases (95.8 per cent) showed varying degrees of impairment of hearing: complete loss was found in one hundred and seven and partial in thirty-two. The impairment of hearing was almost invariably homolateral but in five cases it was bilateral. In cases showing partial involvement, the deafness was more marked for higher tones in the ear on the affected side (audiogram no. 1) as com-

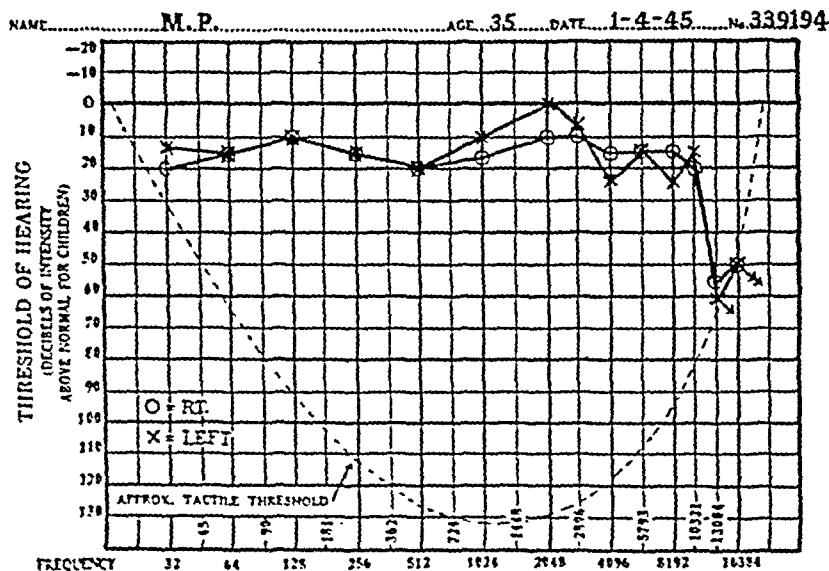
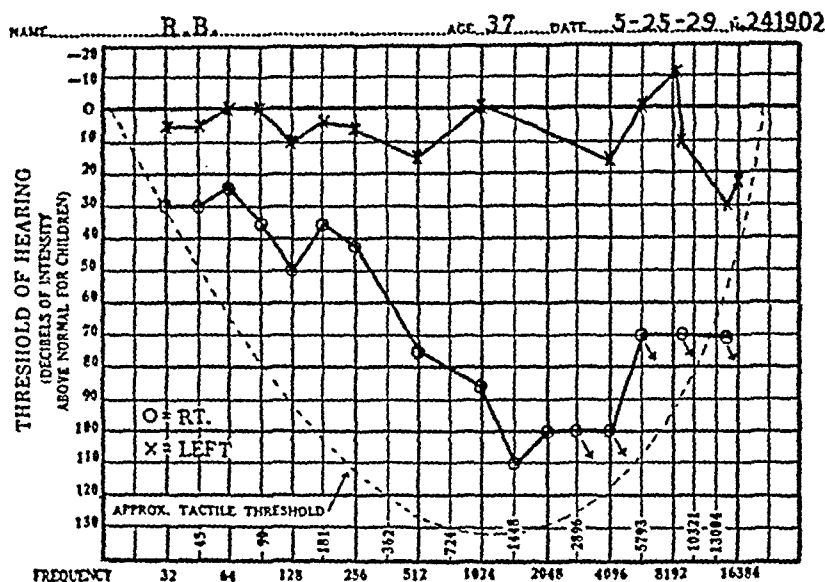


FIG. 1. Audiogram No. 1: Typical changes in a unilateral acoustic neurinoma.
Audiogram No. 2: Acoustic neurinoma without hearing loss.

pared to the opposite ear. This difference is really more marked than the usual deficit we see in otherwise normal middle-aged individuals. In five cases there was no significant change in the audiogram (audiogram no. 2), but vestibular tests were absent on the affected side. A typical case of this anomalous group is summarized briefly as follows:

Case no. 136. M. P., W. F., 35, Hist. no. 33919. Admitted December 26, 44 with the history of intermittent bifrontal headaches for ten years. These headaches were mild in the beginning and the patient did not think much of them until a few months before admission when they became more severe, more or less constant, this time localized in the left suboccipital region with radiation to the frontal region of the same side. For three months previous to admission there had been some diminution of vision. No history of nausea, vomiting or acoustic disturbances. Neurologic examination on admission revealed bilateral papilledema, 2-3 D., questionable diminution of the left corneal reflex which was considered as normal by other observers, and rotary nystagmus which was more pronounced on looking to the left. Audiograms revealed a normal hearing. Vestibular tests were not performed. X-rays of the skull, normal. A ventricular air injection was performed on the 27th of December and the ventricles appeared normal in size with no shift and no evidence of obstructive lesion. On December 29th a lumbar puncture was performed to determine the degree of pressure and was found to be 450 mm. of c.s.f. The diagnosis of pseudotumor cerebri was made and on the 30th of December a subtemporal decompression was performed. On the fourth post-operative day a peripheral facial paralysis developed on the left side. Vestibular tests were then performed and there was no response on the left. The presumptive diagnosis of acoustic neurinoma was then made and on the 5th of January she was operated on by the unilateral cerebellar approach on the left and a tumor was found at the angle arising from the VIIIth N. Weight: 12.5 gms. Histological diagnosis: Neurinoma.

In this case the true nature of the intracranial process could have been diagnosed properly had the caloric test been performed in the beginning. This does not mean that the vestibular response is expected to be diminished or absent in every case of acoustic neurinomas because this is not true as we shall see later.

b. Vestibular: It is unfortunate that vestibular tests were not performed in all cases, as the diagnosis in most of them was so obvious that it did not appear necessary to subject the patient to additional diagnostic procedures. The cold caloric test was invariably used, and was performed in eighty-seven cases, seventy-seven (88.6 per cent) of which had impairment of the vestibular function on the same side of the lesion. In sixty-six the loss was total and in eleven partial. There was bilateral impairment of function in five and in one case the loss of function was contralateral to the side of the hearing deficit. In ten cases there was no loss of vestibular function but the hearing was definitely affected.

From the foregoing we must conclude that in neurinomas of the VIIIth N. we must expect involvement of both the cochlear and the vestibular branches, or at least one of them. This conclusion follows closely the results of Henschen and Cushing, diverging from the views of Bárány (2), and Olsen and Horrax (25) who claimed that we should invariably expect disturbances of the vestibular fibres. Others go even further in stating that these tumors, therefore, must originate primarily from the vestibular component. This last statement, we believe has been convincingly disproved by the work of Hardy and Crowe (17), who upon examining serial sections of temporal bones in two hundred and fifty autopsies found small acoustic tumors in six, the vestibular nerve being involved in four and the cochlear in two.

Other cranial nerves: Involvement of other cranial nerves was quite rare in our series. There was objective evidence of loss of sensation of the palate in ten cases. Ipsilateral paresis of the palate in thirteen and of the vocal cord in six. The XIth N. was even less often affected, occurring in only six cases. Atrophy of the tongue on the affected side was present in three instances.

Cerebellar signs: a. Nystagmus: Although there is still some debate about the source of nystagmus in acoustic tumors, it is the general consensus of opinion that its origin is definitely cerebellar. As pointed out by Ford (13), in nystagmus of cerebellar origin the eyes tend to seek a rest point situated from 10 to 30 degrees from the midline on the side contralateral to the lesion. On looking to the affected side, a coarse horizontal nystagmus is observed in which the slow phase is towards the rest point, but when the eyes are moved beyond the rest

point on the contralateral side, a finer, more rapid nystagmus is seen. The slow phase is again to the rest point. Ford states, furthermore, that this is a fixation nystagmus as is reduced or abolished when the eyes are covered and, therefore, may be distinguished from vestibular nystagmus by the fact that in the latter the slow phase is always toward the injured side and that it is increased by preventing fixation. Almost invariably our cases are described as showing these characteristics and this is the main reason for including nystagmus as a cerebellar sign. Although a common finding in this series, it is not constant. It was present in one hundred and five cases (72.4 per cent). The nystagmus was mainly of the coarse horizontal type (nine-three cases), rotary nystagmus being quite infrequent and occurring in only twelve cases. There was not a single instance of vertical nystagmus in our series.

b. Incoordination: Incoordination of cerebellar origin was as frequent an objective finding as the signs referable to the trigeminal nerve. It was found in one hundred and twenty-five cases (86.2 per cent). Incoordination usually affected the arm and leg on the affected side (sixty-nine cases), being bilateral in ten and affecting the homolateral arm alone in eleven. Both arms were involved alone in three and the homolateral leg was affected solitarily in one. The Romberg was positive in sixty one and the gait was definitely ataxic in one hundred and fourteen cases.

Pyramidal changes: They were relatively rare and usually occurred in well advanced cases where there was definite indication of pressure on the brain stem. They were present in twenty-seven cases (19.6 per cent), being contralateral to the lesion in nine, on the same side in eight and bilateral in ten.

Sensory changes: Sensory changes in the body and extremities were even less common and were present in only seven cases (4.8 per cent) being ipsilateral in four, contralateral in two and bilateral in one.

Roentgenological diagnosis: In every case where the diagnosis of an acoustic tumor was suspected, stereoscopic films of the base of the skull were taken in an attempt to visualize the porus acusticus, the Towne's position being rarely used. Unfortunately, we were able to find reports in only one hundred and fourteen cases. Of these, fifty-two (50 per cent) showed either enlargement or definite destruction of

the internal auditory orifice, seven showed just evidence of increased intracranial pressure as evidenced by destruction of the sella turcica



FIG. 2. X-ray of the base of the skull (M. R. Hist. No. 300471) showing marked destruction of the left porous acousticus from an acoustic neurinoma.

and increase in the convolutional markings. Forty-five cases did not show any abnormalities. (See Fig. 2.)

Air studies were rarely performed, being done in eight cases where the diagnosis was in doubt. Ventriculography was used in all of them. In five of these cases the ventricles were markedly dilated with definite evidence of a block at the aqueduct of Sylvius. In one case there was moderate dilatation of the ventricular system with no evidence of block or any other deformity. In two cases the ventriculograms were completely normal, showing small symmetrical ventricles with no evidence of obstruction. In none of these cases could the deformity of the ipsilateral occipital horn as described by Stone and Schulze (29) be visualized.

Lumbar Puncture: As lumbar punctures are definitely contraindicated in neoplasms of the posterior intracranial fossa for obvious reasons, they were not done in any except in one case, summarized elsewhere, in which the diagnosis was in doubt, the lumbar puncture being done with the sole purpose of measuring the pressure. As no fluid was withdrawn there was no report of its protein content, which has been found increased in many instances by others.

Ventricular Size: An approximate estimate of the size of the ventricles could be obtained in seventy-eight cases by tapping the occipital horns through posterior trephines as a preliminary step in the actual operative procedure. Forty-seven (60.3 per cent) showed marked dilatation of the ventricles. Moderate dilatation was present in thirteen (16.6 per cent). In one case the ventricles were slightly dilated. In five (6.4 per cent) they were found to be normal in size, and in twelve (15.4 per cent) they appeared quite small. No accurate estimate of the ventricular pressure was obtained, the only criterion being the objective degree of force displayed by the fluid on tapping the ventricles. Marked pressure was reported in sixty-two cases (82 per cent) and the pressure was considered normal in fourteen (18 per cent).

Weight of the tumor: It was not possible to obtain a true idea of the weight of the tumor because in about 75 per cent of the cases it was cystic and in many instances the cystic portion represented its major bulk. So the figures we are giving represent the solid contents of the tumor, including the capsule. Weights were recorded in one hundred and thirty-five cases, the smallest being 1 gm. and the largest, 70 gms., with an average of 18.9 gms. The weight of the tumor itself did not

have special bearing on the technical part of the operation as we find cases in which the larger tumors were easier to remove than the deep-seated smaller ones. However, it seems that the weight of the tumor has some relationship with the ultimate operative result, as we shall see later.

Operation and Operative Mortality: In discussing the operative technique and mortality in this series, we consider it worth while to make a brief review of the evolution of the modern operative technique as developed by Dandy. Cotterill (3) was perhaps the first to use the bilateral cerebellar exposure, but it was not until Cushing's introduction of the crossbow incision (4) that an adequate exposure of the cerebellum could be obtained. Krause's (20) improvement on the unilateral approach introduced by Woolsey (33), but previously used by others, although used with disastrous results in the removal of acoustic tumors, offered a valuable contribution to the ultimate development of Dandy's method. Up to Cushing's time, every attempt in removing these tumors was a depressing one and his contribution of intracapsular curettement (4) was the most important contribution up to that time. In his monograph on acoustic tumors he doubted whether these tumors could ever be totally enucleated with satisfactory results. Shortly afterwards, Dandy (6) published his preliminary report on the total extirpation through the bilateral cerebellar approach by painstaking dissection of the capsule after intracapsular evacuation of the contents. A few years later Dandy (10) modified the crossbow incision and introduced the transverse incision for bilateral exposure of the cerebellum which curved downward at both mastoid processes. This approach provided the same exposure and made the visualization of the angle easier because the nuchal muscles fall away from, rather than toward the line of vision and, furthermore, avoided the cerebrospinal fluid fistula which frequently occurred in the vertical part of the crossbow incision. Even with this improved procedure, however, he observed that the degree of trauma inflicted on the cerebellum by retraction was great and subsequently adopted the method of uncapping the cerebellum as first suggested by Frazier (14). The degree of exposure to the angle was therefore greater and the damage to the cerebellum less. In the early 30's (8) he found and extirpated a few tumors at the angle through the unilateral approach which was intended for sectioning

the sensory root of the Vth N. at the pons, as these patients complained of tic douloureux on admission. He observed that this procedure was feasible and entailed even less damage and post-operative edema to the cerebellum and brain stem.

From all these observations originated Dandy's classical unilateral procedure introduced in 1934 (11) and which is briefly summarized as follows: 1. same unilateral incision as used for Ménière's disease and tic; 2. bone rongeué as far laterally as possible without entry to the mastoid cells and anteriorly to the lateral sinus; 3. tapping of the posterior horn of a lateral ventricle through a previously placed occipital trephine in the opposite side; 4. evacuation of fluid from the cisterna magna and spinal canal; 5. excision of the outer cap of the cerebellum; 6. intracapsular evacuation of the solid contents; and 7. careful, painstaking dissection and removal of the capsule. This procedure has been almost universally adopted and the general trend of most neurosurgical clinics at present is to remove these tumors in toto according to the method evolved by Dandy after so many years of toil.

By taking a quick glance at the following table on operative technique and mortality, we may see then why it was necessary to make the foregoing discussion as the operative mortality diminishes with the ultimate perfecting of the method of attack. As explained at the beginning of this presentation, almost all the neurinomas at the cerebellopontile recess were operated on by Dr. Dandy. One of the acoustic neurinomas was operated on by someone else and four were recurrences operated on originally at other clinics and therefore we consider it fair enough not to include these cases here, lowering the number of cases, consequently, to one hundred and forty.

In all of these cases the tumor was totally removed in one stage. As we see the over-all mortality for twenty years, including the different operative techniques, was of 22.1 per cent, which diminishes to 6.5 per cent when the unilateral approach with uncapping of the cerebellum and careful dissection of the capsule was done, representing a tremendous difference. This last figure represents the operative mortality during the last eight years (sixty-two cases), dropping to 2.4 per cent (1 fatality in forty-one cases) in the past five years. On the other hand, we may easily observe that the mortality rate is

tremendously high whenever the finger was used, no matter what the method of attack was. The operative mortality in these cases ranged from 40 to 100 per cent; therefore, this procedure cannot be too

TABLE 2

*Operative Technique and Mortality in 140 Cases of Unilateral Acoustic Neurinomas—
Total Extirpation*

OPERATIVE TECHNIQUE	NO. CASES	LIVED	DIED	MORTALITY (%)
1. Bilateral Cerebellar				
A. No cerebellar cap				
a. Finger enucleation alone.	5	2	3	60
b. Intracapsular + finger enucleation.	4	1	3	75
c. Intracapsular + careful dissection.	30	22	8	26.6
B. Cerebellar cap removed				
a. Finger enucleation alone.	2	0	2	100
b. Intracapsular + finger enucleation.	1	0	1	100
c. Intracapsular + careful dissection.	12	11	1	8.3
2. Unilateral Cerebellar				
A. No cerebellar cap				
a. Finger enucleation.				
b. Intracapsular + finger enucleation.				
c. Intracapsular + careful dissection.	13	10	3	23
B. Cerebellar cap				
a. Finger enucleation.	1	0	1	100
b. Intracapsular + finger enucleation.	10	6	4	40
c. Intracapsular + careful dissection.	62	58	4	6.5
Total for twenty years.	140	110	31	22.1

forcibly condemned, as no matter how careful we are, a certain amount of trauma is certain to be inflicted on the brain stem, and even a small amount may bring about disastrous consequences.

Analysis of Operative Deaths: a. Sex: Surprisingly enough, the mortality among men was greater than in women, in a proportion of

3:2, this proportion being greater if we consider that in the whole series females were affected much more frequently than males.

b. Age: The age did not have any bearing on the mortality rate and occurred between the ages of 23 and 65, with an average of 43.6 years, which approaches closely the average age on admission for the whole group.

c. Symptoms: There was no striking correlation between the symptomatology and the operative mortality, death occurring with equal frequency in patients with early and those with advanced symptoms. The average duration of symptoms in our fatalities, however, was slightly above the general average for the series, being 5 years, the shortest 3 months and the longest 18 years. On admission twenty-three patients were alert and cooperative, four comatose and three totally blind.

d. Weight of the tumor: The average weight of the solid contents of the tumor was 27.6 gms., the smallest 2 gms. and the largest 55 gms. The average weight is certainly much higher than in the whole group, which might tend to prove that the bigger the tumor, the greater the amount of pressure on neighboring structures, and the greater the degree of obstruction in the ventricular system, hence, making the final result of the operation more uncertain.

e. Time of death: The majority of these patients died within twenty-four to forty-eight hours after the operation, only one of them dying while on the operating table. These early deaths showed the usual signs of damage to the brain stem, as hyperthermia, tachycardia, laboured respirations, profound unconsciousness and tonic fits. The late fatalities occurred between the third and thirtieth post-operative day and were fewer in number, death being due usually to pneumonia or secondary infection.

f. Cause of death: Autopsy was performed in almost every instance but the cause of death, however, was not clear in three of them. For purpose of simplification we have divided the causes of death into four main groups as follows:

1. Direct trauma to the brain stem: Occurred in twelve cases. In practically all of them the finger was used in enucleating the tumor.

2. Meningitis: Four patients died of meningitis, death occurring quite late, an average of four weeks after the operation. In two of

them the mastoid cells were accidentally opened in rongeur-ing the bone. It should be mentioned that these deaths occurred before the era of the sulfones and the newer antibiotics.

3. Pulmonary: One patient died from pulmonary embolism and five from aspiration pneumonia, a direct consequence of paresis of the palate. Death from pulmonary causes occurred within the first two weeks post-operatively.

4. Vascular: These deaths were direct consequence of accidental ligation of vital arterial supply to the cerebellum and brain stem. In two cases the basilar artery was partially clipped, the patients dying six hours and three days, respectively, post-operatively. In two other cases the posterior inferior cerebellar artery was ligated, death occurring within the first forty-eight hours after operation. One patient died on the fourth post-operative day and at autopsy a large extradural hemorrhage was found at the operative site. Thrombosis of the left lateral sinus was found in another patient who died on the third post-operative day; the cause of death in this case is quite debatable, however, as one may ligate a lateral sinus with no impairment of function.

End Results: Efforts have been made to contact every living patient, in itself a rather hazardous task. Up to the time of this communication follow-up studies have been possible in only seventy-six cases covering a period from one to eighteen years. There have been six deaths in these cases, four of which we feel are direct sequelae of the operation, giving a late case mortality of 5.2 per cent. In three of these patients post-mortem examination was performed: in two of them a marked hydrocephalus due to occlusion of the foramina of Luschka and Magendie was apparent, death occurring one and eight years, respectively, after the operation. One patient developed cerebrospinal fluid rhinorrhea shortly after the operation, followed later on by cerebrospinal fluid otorrhea and died one year later from meningitis: at autopsy a definite perforation was found on the petrous bone. In one patient no autopsy was performed, but in about six months after the operation she started to become confused and showed gradually signs of increased intracranial pressure. Her symptomatology was almost a replica of the other two patients who showed occlusion of the foramina at the base.

It is curious that in three of these patients there was evidence of internal non-communicating hydrocephalus produced by occlusion of the foramina of Luschka and Magendie. This might be explained simply on the basis of a basilar arachnoiditis due probably to a low-grade post-operative meningitis not virulent and severe enough to produce septic symptoms, although it also might be due to direct trauma, to the electrocautery or to slight post-operative bleeding with subsequent organization.

Recurrences: In the seventy-six cases which we were able to follow there was one recurrence, this occurring eleven years after the total extirpation of the tumor. This case represents the only instance in which a second operation was performed in this series.

Preservation of Facial Function: In total extirpation of acoustic neurinomas preservation of facial integrity is quite a difficult task, due to the close proximity and marked distortion of the VIIth N. by the neoplasm and its consequent injury during operation. The ultimate preservation of the VIIth N. we consider as a vital step in the removal of these tumors due to the future disability entailed by a disfigured face when the patient tries to resume his previous occupation. Besides the cosmetic reasons we should also bear in mind the possibility of corneal ulceration in an anaesthetic eye with a Bell's palsy. In this series, unfortunately, the facial nerve was preserved in only nine cases.

To obviate the facial disfigurement spino-facial anastomosis was performed in practically all the cases with post-operative facial paralysis. Good functioning of the anastomosis was obtained in 95 per cent of the cases. This return of function, however, is quite relative, as in most cases the facial movements have to be controlled by movements of the shoulder, a task that requires plenty of practice and the cooperation of an intelligent patient. Even then, the facial movements obtained are quite grotesque, coming in the form of a mass reflex of the whole musculature of one side of the face.

In twenty-one cases the spino-facial anastomosis has been combined with a plastic operation in the face by means of transplants of fascia lata strips insuring a satisfactory anchorage between the temporal fascia and the periorbital and perioral muscles at the nasolabial fold. The technique has been described by Hanrahan and Dandy (16)

several years ago. This corrective measure, we believe, affords the best cosmetic results. The nerve anastomosis is necessary to preserve muscle tone and the fascial transplant is important in correcting the flatness and asymmetry of the face at rest, not corrected by anastomosis alone. (See Fig. 3.)

The ultimate goal should be, therefore, the total preservation of the facial nerve at operation. This has been advocated by Olivecrona (24)



FIG. 3. I. S. Hist. No. 255497 showing the result of a combination of spino-facial anastomosis and plastic operation on the face. Left: Face at rest. Right: Movement of the left face controlled by raising the shoulder. (Courtesy of Hanrahan, E. M., and Dandy, W. E.: A procedure to correct facial paralysis. J. A. M. A., April 8, 1944, 124: 1051-1053)

who was able to preserve the anatomical continuity of the nerve in 65.2 per cent of his cases by careful electrical stimulation of the under-surface of the tumor during dissection of its capsule. If this entails, however, leaving part of the tumor adherent to the nerve we should not hesitate to sacrifice the nerve as a recurrence would appear inevitable.

Comments: In summarizing, we have shown that the unilateral acoustic neurinomas, without evidence of neurofibromatosis elsewhere in the body, represent the most common type of neurinoma at the cerebellopontile recess, and they occur predominantly in females.

The average age at the onset of symptoms was 39.6 years, with an average duration of symptoms of 4.5 years.

Only 31 per cent of the cases followed the chronological order postulated by Cushing; in 69 per cent this order was changed in different fashion. This great variation may be easily explained by variation in the degree and direction of the growth and by individual anatomical differences at the angle.

In the greatest number of instances there was subjective and objective evidence of involvement of the VIIIth and Vth nerves, as well as the cerebellar pathways. The VIIIth N. was involved in every case, either by affection of both components or by solitary involvement of either the cochlear or vestibular branches. In certain instances only the VIIIth N. was affected alone, the patients presenting on admission Ménière's syndrome, which although uncommon with tumors at the angle, does occur and therefore is worthwhile to remember in the differential diagnosis of this disease.

Tic douloureux was the only complaint in many instances, but in this series was always accompanied by some loss of hearing, which one is liable to neglect if we consider the late age in which this symptomatology was present in our cases. Audiometer and vestibular tests are, therefore, in order in every patient with tic douloureux. These tests, however, are of no value in other kinds of tumors at the angle producing tic douloureux; e.g., pearly body tumors, as has already been shown in another communication, due to the fact that the VIIIth N. is not primarily affected.

The diagnosis may be made clinically in most of the cases. X-ray evidence of destruction of the porus acoustics was present in only 50 per cent of the cases and when absent was not, therefore, absolute proof against a positive diagnosis. Ventriculography was rarely indicated, and when done showed either symmetrical dilatation of the ventricular system, a block at the aqueduct or perfectly normal ventricles.

The best method of operative attack of these tumors is by the procedure devised by Dandy. Enucleation of the tumor with the finger cannot be condemned too strongly because of the trauma inflicted on the brain stem. The mortality is usually very low if careful and painstaking dissection of the capsule is performed.

Early operative mortalities are predominantly due to one of four causes, namely: 1. trauma to brain stem, 2. vascular occlusion of vital arteries in the posterior fossa or post-operative bleeding, 3. meningitis as direct sequela to opening of the mastoid cells, and 4. aspiration pneumonia. Late mortality, on the other hand, might occur years after the operation due to cicatricial closure of the foramina of Magendie and Luschka, an internal non-communicating hydrocephalus being the end result.

The ultimate goal of any operative procedure should be the preservation of the facial nerve. When this is not possible, a spino-facial anastomosis combined with a plastic operation on the face should be the method of choice.

UNILATERAL ACOUSTIC NEURINOMAS AND VON RECKLINGHAUSEN'S DISEASE

The uncommon coexistence of unilateral acoustic neurinomas and peripheral von Recklinghausen's disease has already been mentioned. In the whole group we were able to find only three cases of unilateral tumors with evidence of peripheral neurofibromatosis (1.8 per cent).

One male and two females were affected. The average age on admission was much shorter than in the previous group, being 24.3 years, 22 the youngest and 26 the oldest. In one case the peripheral neurofibromas were noticed 1 year before the onset of intracranial disturbances, in another one the cranial nerve symptoms preceded the appearance of the peripheral tumors by two years and in the third case the peripheral lesions were noticed on admission and no definite history could be obtained about the time of their appearance. The average age at onset of intracranial manifestations was 14.3 years, the earliest being 9 and the oldest 20 years. The duration of symptoms was 10 years, and, therefore, twice as long as in the preceding group. There was no history of trauma or infection.

Symptomatology: In none of these cases could we find a constant chronology of symptoms. Auditory, cerebellar and trigeminal manifestations represented the initial symptom in each respective case. In all cases, however, the outstanding symptoms were auditory and cerebellar.

The auditory manifestations were characterized by gradual diminu-

tion of hearing in two, and sudden unilateral deafness in one. There was bilateral impairment of hearing in one in which the possibility of bilateral lesions was suspected but never corroborated as the unilateral approach was used at operation. Tinnitus was present in two, coming in one of them simultaneously with the impairment of hearing and in the other one it followed the auditory deficit. There were no vestibular disturbances with the possible exception of one patient who complained of nocturnal loss of balance.

Cerebellar disturbances were prominent in the three cases and always occurred on the same side as the lesion.

Subjective disturbances to the Vth N. were present in two cases, in one of which they preceded the auditory manifestations by nine years and one wonders whether this case represented primarily a tumor arising from the Vth N. or not. In the other case it followed the hearing loss by six months. Not a single patient complained of headache.

Facial weakness was noticed subjectively by one patient, occurring six months after the onset of auditory manifestations. There were no subjective manifestations referable to other cranial nerves.

Symptoms referable to the spinal cord and characterized by spastic weakness of the extremities with typical mass withdrawal was present in one case, indicating the multiplicity of lesions in the central nervous system. They occurred rather late and followed the auditory manifestations by 3.5 years.

Signs: Subcutaneous nodules were prominent in the scalp, upper extremities and trunk. All patients were well-oriented and alert on admission.

Papilledema was present in one. Involvement of the IIIrd and VIth nerves was present in one case, the involvement occurring in the same side as the lesion. All patients showed a diminished corneal reflex and impaired sensation of the face on the same side as the lesion. In one case there was involvement of the motor branch of the Vth N. Facial paralysis of the peripheral type, incomplete, was present in two.

The neurogenic type of deafness was corroborated in all, being bilateral in one. It was total in two and partial in one. Caloric tests were performed in only one case which showed bilateral loss of vestibular response.

Cerebellar signs could be elicited in only two cases, in spite of the fact that all gave a history of subjective involvement of the cerebellar pathways. Nystagmus was not a constant finding and was found in only one case. It was of the horizontal type. Involvement of the IXth, Xth, XIth and XIIth nerves was present in one case, which showed in addition involvement of the spinal cord, as evidenced by motor weakness of all extremities with bilateral pyramidal signs and a sensory level to T4.

Roentgenological diagnosis: X-rays were taken in all cases. In two of them there was marked destruction of the porus acousticus and in one they were negative. Air studies were not performed.

Ventricular Size: Ventricular estimation was performed in two cases, one of which showed marked dilatation of the ventricles and the pressure was said to be greatly increased. In the other one the ventricular pressure was normal and the ventricles were relatively small.

Operation, operative mortality and end results: As the predominance of symptoms and signs was present on the right side in all cases the unilateral cerebellar approach was performed in all. The cerebellar cap was resected but the curettement of the contents was extremely difficult, due to the marked hardness of the tumor. Erosion of the acoustic foramen was corroborated in all. In only one case the tumor seemed to arise from the Vth N., this case being the one in which subjective disturbances of the sensory branch of the Vth N. were present nine years before the onset of auditory manifestations. One patient died seven years later with signs of marked involvement of the spinal cord, with no indication of intracranial recurrence. Another patient died on the fourth post-operative day with signs and symptoms pointing to trauma of the brain stem. The other patient is living and well at the end of six years.

Comments: Only three cases of unilateral acoustic neurinomas associated with peripheral neurofibromatosis were found in this series. The age at onset of intracranial disturbances was far below the age of patients with solitary neurinomas, e.g., 14.3 years, and the duration of symptoms was quite prolonged (ten years). There was no specific chronologic order of symptoms but the auditory, trigeminal and cerebellar manifestations were quite predominant and the first two were objectively constant. Only one patient showed involvement of the

spinal cord. The operation was quite difficult in all cases, due to the extreme hardness of the tumors which would make their curettement a very difficult procedure. The final outcome in these cases is not a happy one, as they have been reported to be associated with multiple meningiomas or other neurinomas within the intracranial chamber or along the spinal canal.

BILATERAL ACOUSTIC NEURINOMAS

Six cases (3.7 per cent) of bilateral tumors of the nervus acusticus were found in our series, five of which were verified either at operation or autopsy, and in the other one they were suspected because of the bilateral signs and early age of the patient. In this last case the opposite side was not explored at operation and the patient died a few hours later. Unfortunately, no autopsy was performed.

Etiology: It is thought that these tumors when bilateral are congenital, because of the relatively young age of the patients and their common hereditary transmission according to the laws of Mendel. In two of these patients, who were sisters, there was a history of bilateral acoustic neurinomas in the maternal side of the family in approximately thirty-five members since the eighteenth century, the persons so affected having complained of bilateral deafness, and having died relatively young, approximately five years after the onset of symptoms.

Their relationship to von Recklinghausen's disease seems more obvious than in the case of unilateral neurinomas. Three cases (50 per cent) showed evidence of peripheral involvement elsewhere in the body.

Incidence: Males and females were equally affected. The average age on admission was 23 years, the youngest 14 and the oldest 33. The average age at onset of symptoms was 17.8 years, the youngest 9 and the oldest 29. As pointed out earlier, these figures resemble very closely those found in the unilateral tumors with evidence of neurofibromas elsewhere in the body. The duration of symptoms, however, was much shorter, being 5 years.

Subjective manifestations: The initial symptom in four was that of increasing deafness, while in the other two the manifestations were represented by subjective evidence of increased intracranial pressure and involvement of the cerebellar pathways, respectively.

All patients but one gave a history of impairment of hearing bilaterally, one ear being affected first in three and both ears simultaneously in two. The other patient gave a history of impairment of hearing on one side, but the audiogram on admission showed also moderate diminution of hearing on the opposite side. Tinnitus was present in one case; it was unilateral and appeared three years after the onset of other auditory symptoms. History of vertigo was obtained in two, in one of which it was just a subjective sensation of dizziness and in the other one of true rotary type. It appeared one month and two years, respectively, after the onset of deafness.

Cerebellar symptoms were present in every case. They followed auditory and labyrinthine symptoms but in one case preceded them by two months. The usual complaint was staggering on walking.

Headache was not a common symptom, being present in only one case. This patient complained of bifrontal type of pain without history of suboccipital discomfort. There was no subjective evidence of involvement of the Vth N., although objective findings were present in three.

Hoarseness and dysphagia were present in one case, appearing three years after the onset of symptoms. Subjective manifestations of increased intracranial pressure were present in four, in one of which it was the apparent initial symptom, being a late manifestation in the other three.

Objective findings: There was objective bilateral impairment of hearing in all cases (Fig. 4). Total bilateral deafness was found in four and unilateral deafness with moderate degree of hearing impairment on the opposite side was found in two. The neurogenic type of deafness was corroborated in all cases. Vestibular tests were performed in five. They showed preservation of vestibular response bilaterally in one case, diminished bilateral response in three, and absent vestibular response on only one side in another.

Cerebellar signs such as ataxia of the extremities and staggering gait were present in all cases. They were bilateral in four and unilateral in two. Horizontal nystagmus was elicited in five with equal amplitude on looking to either side.

Sensory changes on the face were present in four cases with accompanying diminution of the corneal reflex. These signs were present bilaterally in two of the cases.

Facial weakness was elicited in five cases. It was unilateral in three and bilateral in two. As it is the case in most of the neurinomas of the posterior fossa, this peripheral weakness was incomplete in the affected cases. The IXth and Xth N. were involved in only one case, the affection being bilateral. There was no involvement of other cranial nerves.

Pyramidal signs were present in one case, the involvement being bilateral. There were no sensory changes.

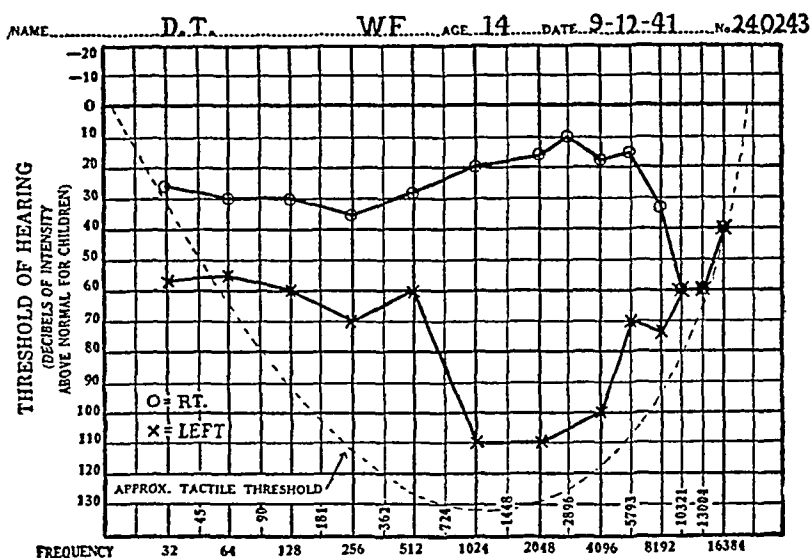


FIG. 4. Audiogram in a case of bilateral acoustic neurinoma. Hearing is bilaterally diminished, more so on the left.

X-rays: Roentgenologic examination of the skull was reported in four cases. In one there was evidence of erosion of the porus acusticus on both sides (Fig. 5). Another one showed an unilateral erosion and the other two showed no apparent changes. There were no air studies performed in any of the cases.

Ventricular size: Considerable hydrocephalus was found in two cases, moderate enlargement in one and small ventricles in another one. No report of the size of the ventricles could be found in the other two cases.

Operation, operative mortality and end results: The operative approach is rather difficult in these tumors, as the operating space is greatly



FIG. 5. X-ray of the base of the skull (G. W. Hist. No. 335824) in a case with bilateral acoustic neurinomas erosion at both acoustic meati.

reduced due to the presence of tumor on both sides and the subsequent edema of the cerebellum and brain stem upon attempting removal of these tumors. Consequently the mortality is high as is shown in the following brief operative summary of these cases.

Case No. 1: Unilateral approach without resection of the cerebellar cap. Enucleation with the finger. Suspected of having a bilateral tumor due to bilateral symptoms, but only one side was explored, from which a large tumor was removed. Patient died seven years later at another hospital from bronchopneumonia and gangrene of the lungs. At autopsy, in addition to the pulmonary pathology, an acoustic neurinoma was found on the opposite side.

Case No. 2: Unilateral approach without cerebellar cap. Enucleation with the finger. Bilateral tumors were not suspected in spite of the bilateral impairment of hearing. Tumor on one side completely removed. Returned four years later with clear-cut signs pointing to a lesion in the opposite side with complete deafness. Operation showed a large acoustic tumor in the opposite side which was removed in toto. Uneventful recover, except for bilateral facial paralysis and paresis of vocal cords.

Case No. 3: Bilateral cerebellar with bilateral section of cerebellar cap. Enucleation with the finger. Bilateral removal of the tumor in one stage. Death in 48 hours. Autopsy revealed diffuse softening of the brain stem.

Case No. 4: Unilateral cerebellar with removal of cerebellar cap, intracapsular curettement and careful dissection of the capsule. Tumor successfully removed in one side. As the patient gave familial history of bilateral tumors (patient is sister of Case No. 3) and had bilateral signs it was recommended that she report in six weeks for a second operation. Patient did not report until six months later, with total blindness. Operation of the other side was not recommended.

Case No. 5: Bilateral cerebellar, resection of the cerebellar cap. Enucleation with the finger. Tumor completely removed in one side. It was visualized in the other side but not removed as a second operation was contemplated. Patient died on the third post-operative day. No autopsy.

Case No. 6: Bilateral cerebellar. Cerebellar cap not resected. Enucleation with the finger. Tumor totally removed in one side. Although the patient had bilateral signs it was not considered advisable to explore the opposite side. Patient died a few hours later. No autopsy.

Comments: From this summary of cases with bilateral neurinomas one may conclude that these tumors do not represent diagnostic problems. In the first place they occur in young individuals, the average age at onset being 17.8 years. The duration of symptoms is more prolonged than in the solitary acoustic neurinomas and much shorter than in acoustic neurinomas with peripheral neurofibromatosis. In half of these tumors there is evidence of peripheral neurofibromas and there seems to be a very definite familial predisposition. The symptomatology is typically characterized by bilateral diminution of hearing which may be accompanied by other bilateral signs.

The operative attack on these tumors presents a rather difficult problem due to the reduced operating space and the subsequent greater edema of the brain stem and cerebellum. Therefore, the operative mortality is high. The best method of approach, we believe, is the bilateral cerebellar with extirpation of the tumor in two stages. As in the solitary acoustic neurinomas, the enucleation of the tumor should be done in a painstaking manner, as the trauma inflicted on the brain stem would be much greater when the finger is used in their removal.

Case No. 3: G. W., W. F., 24, Hist. No. 335824. Admitted on the 27th of October 1944, with the chief complaint of progressive deafness for five years. The family history revealed that ever since the eighteenth century, the Campbell family, maternal side, had suffered from bilateral deafness and premature death. There did not seem to be any predilection for sex; the onset of auditory disturbances always started between the ages of twenty and thirty years, every member so affected dying five years after the onset of symptoms. The present patient knew of thirty-five of her maternal ancestors who died in this manner. Of her immediate family she remembered that her mother died at the age of 34, an uncle at 32 and her grandfather at 30. A sister of thirty-two years (Case No. 4) had been suffering from bilateral deafness and ataxia. The onset of symptoms of this patient started five years previously and was characterized by progressive diminution of hearing on the right. Exactly one year after the onset she suddenly found that she was completely deaf in both ears and for the first time clumsiness in the arms and slight staggering on walking was noticed. These symptoms, however, remained stationary until one year before

admission when she started to complain of dysarthria and dysphagia along with fleeting and sudden episodes of blindness on stooping. Five months before admission she noticed some weakness of the left side of the face, which also appeared on the right side shortly afterwards. Physical examination on admission was essentially negative, except for scattered "café au lait" spots on the trunk and abdomen. Neurologic examination revealed marked diminution of visual acuity bilaterally. 6 D. papilledema in both fundi. Bilateral diminution of the corneal reflexes with hypaesthesia and hypalgesia in both sides of the face. Bilateral facial weakness, peripheral, incomplete. Horizontal nystagmus with equal amplitude on looking to either side. Bilateral total deafness. Absent vestibular response on the right and markedly diminished on the left. Absent pharyngeal reflexes on both sides. Marked dysmetria and asynergia of all extremities. Staggering gait. Positive Romberg. Moderate spasticity of all extremities with hyperactive deep reflexes, bilateral Hoffman's and Babinski. X-rays of the skull: marked dilatation of both internal acoustic meati. Operation (Oct. 28-44): Bilateral cerebellar approach. Removal of cerebellar cap. Typical neurinomas found at each angle. Curettement of the tumors extremely difficult due to pronounced hardness of contents. Enucleation of both tumors with the finger. Weight: Right: 16.6 gms.; left: 10.7 gms. Histological examination: Neurinoma. Postoperatively the patient never regained consciousness. There was marked hyperthermia, rapid, thready pulse and labored respirations. Died in forty-eight hours. Autopsy revealed diffuse softening of the pons and medulla.

NEURINOMAS OF THE VTH NERVE

Neurinomas of other cranial nerves in the posterior fossa are so rare that little attention has been given to them in the classical discussions of this kind of tumors. There are several investigators who may even question the origin of these neoplasms from any other cranial nerve but the VIIIth. In our series of one hundred and sixty cases we have found three tumors (1.8 per cent) arising from the Vth N., two (1.2 per cent) from the Xth and one (0.6 per cent) from the XIth.

The criteria we have used for classifying tumors arising from the Vth N. were that the initial symptoms were referable to the trigeminal

nerve and that this nerve was found at operation to be more affected than the VIIIth N., and we might also add that in some instance there may be a return of auditory and labyrinthine function after the operation. This last criterion, however, is not very convincing as there are several reports in the literature where return of auditory and vestibular functions were noted after operation in typical acoustic neurinomas.

Two females and one male were affected. The lesion was found on the left side in all three cases. The average age at admission was 57 years and the age at onset, 47 years, with an average duration of symptoms of ten years. There was no history of trauma or infection and there was no evidence of peripheral neurofibromatosis.

Symptoms: In these three cases, the initial and predominant symptoms were those referable to the Vth N. and preceded the auditory and labyrinthine disturbances by an average of 4.5 years, the longest 11 years and the shortest 6 months. The chief complaint on admission was that of tic douloureux on the same side in two cases, and subjective numbness of one side of the face in the other. Auditory or labyrinthine manifestations were present in all. Unilateral and gradual diminution of hearing was present in all. History of unilateral tinnitus was present in two, occurring simultaneously with the hearing loss in one and preceding it in the other. Vertigo was likewise present in two and always preceded the loss of hearing. Subjective cerebellar disturbances were elicited in one case, being unilateral and appearing simultaneously with the auditory and labyrinthine manifestations. There were no subjective disturbances of other cranial nerves, nor any pyramidal or sensory changes.

Signs: All patients were alert and cooperative on admission. There were no disturbances of vision and mild papilledema was present in one case. Objective disturbances of the Vth N. were present in two and were characterized by a diminished corneal reflex and hypalgesia on the affected side of the face. The only case that did not show any sensory changes was the one in which the predominant symptom was that of tic douloureux. The VIIIth N. was affected in one case, the paralysis being an incomplete peripheral. There was varying degree of neurogenic deafness in two cases, which was unilateral but no caloric tests were performed in them. Hearing was normal in one

patient who showed complete abolition of the vestibular response. Cerebellar ataxia on the same side as the lesion was present in one case. There were no other neurologic signs.

X-rays were taken in two of them and erosion at the porus acousticus was reported in both.

No data were given about the ventricular size in two cases. The ventricles were moderately dilated in one with marked increase in pressure.

Operation, operative mortality and end results: All these patients were explored, two of them by the unilateral approach and one through a bilateral exploration. The cerebellar cap was resected in two and curettement of the contents plus careful dissection of the capsule was carried out in all. There were no mortalities. All of them showed a complete Vth, VIIth and VIIIth nerve paralysis. However, one patient showed marked return of hearing and complete return of vestibular function two months after the operation. We have been unable to carry out sufficient follow-up studies in these three cases.

Comments: Although neurinomas of the Vth nerve at the cerebello-pontile recess are very rare they do occur, three such cases being reported in this series. The age at onset of symptoms was 47 years, much later than in the acoustic neurinomas, with a duration of approximately ten years, which approaches quite closely the duration of symptoms of unilateral tumors of the VIIIth N. with peripheral neurofibromatosis. Upon admission to the hospital these cases were clinically undistinguishable from the unilateral acoustic neurinomas and the only important differential diagnostic point lies in the fact that trigeminal symptoms preceded auditory and labyrinthine disturbances by an average of 4.5 years.

In two of these patients the initial and predominant complaint was that of tic douloureux and this point stresses again the important relationship of tumors at the cerebellopontile recess in the causation of trigeminal neuralgia. At operation the Vth N. was usually more affected than the VIIIth N., and in one instance there was marked return of cochlear and vestibular functions. This return of function makes one wonder if many of the cases reported in the literature in which such return occurred in supposedly acoustic neurinomas, did not actually represent neurinomas arising primarily from the Vth N.

Case No. 2: J. F., W. M., 67, Hist. No. 255352. Admitted on the 30th of March 1942, with the chief complaint of typical tic douloureux, left, for 15 years. The onset was insidious and characterized by intermittent attacks of paroxysmal lancinating pain on the left side of the face, affecting the distribution of the second and third branches. The pain was infrequent at first but in a few years it became more pronounced and would come at more frequent intervals. From three to four years previous to admission the patient started to complain of gradual and progressive diminution of hearing on the left without tinnitus or dizziness. Six months before admission, slight diminution of hearing on the right. Neurologic examination on admission showed 50 per cent hearing loss on the left and a normal hearing on the right; this partial deafness was found to be neurogenic in type. No caloric tests were performed. There were no other positive neurologic signs. X-rays showed suggestive erosion of the porus acusticus. Operation: March 31, 42: Unilateral cerebellar approach, left. Cerebellar cap was not resected. Deep in the angle and extending between the Vth and VIIIth N. there was a grayish tumor, the size of a hazel-nut, which was completely removed. Porus acusticus was not involved. It was difficult to ascertain from operative report whether the Vth or the VIIIth Nerve was predominantly involved. The Vth N. was sectioned, nevertheless. Weight of the tumor not reported. Histological report: Neurinoma.

NEURINOMAS OF THE XTH NERVE

Two such cases were found in this series and they must be, therefore, extremely rare. One male and one female were affected. On admission the ages were 36 and 54 years, respectively, the age at onset, 29 and 53 years, and the duration of the symptoms, 1 and 7 years. The left side was involved in both cases and there was no history of trauma or infection elicited.

Symptoms: The predominant symptom in both cases was hoarseness which represented the initial complaint in one. Left suboccipital headaches were the initial manifestations in the other case, but hoarseness appeared six months after the onset of the headaches. Disturbances referable to the VIIIth N. were present in one case, appearing two years after the onset of hoarseness. There was no

subjective involvement of the Vth N. In one there was a history of facial weakness which appeared 5.5 years after the onset of hoarseness. Dysphagia appeared 6.5 years later in one and four months later in the other one. Cerebellar manifestations were present in only one case, on the same side as the lesion. Vision was impaired in one. Occipital headaches were present in both; in one, as mentioned above, they represented the initial symptom and in the other they appeared six years afterward. There was no subjective pyramidal or sensory involvement.

Signs: Both patients were alert and cooperative on admission. Only one showed diminution of visual acuity and bilateral papilledema. This patient also showed absent corneal reflex, unilateral analgesia of the face, complete peripheral facial paralysis, complete ipsilateral nerve deafness, paralysis of the ipsilateral vocal cord and palate, weakness of ipsilateral trapezius, sternomastoid and of the same side of the tongue, with cerebellar signs on the side of the lesion. In the other patient (summarized below) there was unilateral paralysis of the vocal cord and palate on the same side as the lesion, these being the only positive neurologic signs on admission.

X-Rays: In only one patient, who showed widespread involvement of the cranial nerves, were we able to corroborate erosion of the porus acusticus.

No data are given as to the ventricular size in any of these cases.

Operation, operative mortality and end result: The unilateral cerebellar approach was performed in both cases with resection of the cerebellar cap, curettement of the contents and complete removal of the capsule. In the case showing only involvement of the Xth N., a small tumor was found arising from the anterior filaments of the Xth N. The other case with marked involvement of the cranial nerves had a rather large tumor weighing 30 gms. The IXth and Xth nerves were lost within the neoplastic mass and the other cranial nerves anterior to it were tremendously pushed forward by the anterior projection of the neoplasm. Both patients were discharged from the hospital in an improved condition. Three and six years, respectively, after discharge, they are vastly improved and have resumed their former occupations.

Comments: Neurinomas of the Xth N. are extremely rare. They occurred in two cases. The age at onset of symptoms was 29 and 53

years, respectively, the duration varying between 1 and 7 years. These neurinomas are easy to diagnose as the predominant and initial symptom is that of hoarseness. At times, however, they might represent diagnostic problems, as in one of our cases in which the only symptom present was hoarseness. If hoarseness is associated with ipsilateral paralysis of the vocal cords a tumor of the Xth N. is a likely possibility.

Case No. 1. I. B., W. F., 54, Hist. No. 237504. Admitted July 29, 1941, with a history of gradually increasing headaches in the left occipital and temporal regions at times of radiating to the lateral aspect of the left side of the neck for one year. These headaches were worse on lying down. One month after onset of headaches she started to complain of intermittent attacks of hoarseness which gradually increased in frequency so that for eight months prior to admission it was constant. For eight months she had some difficulty in swallowing, which had become worse a few weeks before admission. Since onset of symptoms she thought there was also some impairment of taste in the left side of her tongue. On admission the physical examination was negative. The neurologic examination revealed questionable loss of taste in the left side of the tongue, paralysis of the left palate and left vocal cord. There was no hearing loss and no apparent sensory loss in the posterior pharynx. Operation: August 1, 41. Unilateral cerebellar approach, left. The cerebellar cap was not resected. A reddish mass was found in the posterior aspect of the recess, arising from the anterior aspect of the Xth N. The mass was the size of a hickory nut and was removed in toto. Weight: 2 gms. Histological examination: Neurinoma. Patient had a smooth convalescence except for marked dysphagia and hoarseness for a few months. When contacted six years later she was feeling fine and was engaged in her former occupation.

NEURINOMAS OF THE XITH NERVE

Only one case in this group. It was classified under this heading because the initial symptom was that of involvement of the XIth N. in the absence of hearing involvement. In contradistinction with the last two cases there was definite evidence of peripheral neurofibromatosis.

Case No. 1: C. W., W. M., 68, Hist. No. 305730. Admitted on the

27th of October, 1943, with the history that for many years he had noticed a growth on the right thigh. This growth had been removed six years previous to the present admission and proved to be a neurofibroma. For seven years he had also noticed a painless swelling, which did not appear to increase in size, behind the right ear. About 4.5 years before admission he started to complain of stiffness of the left arm with gradual atrophy of the left shoulder girdle. Because of these complaints he was seen six months later at another clinic where the diagnosis of brain tumor was made and the patient was given deep x-ray therapy without relief. About this time he started to notice pain behind the left ear on coughing and sneezing, and some dysphagia. These symptoms increased in the next few years. One year previous to admission he started to complain of hoarseness and incontinence of urine and feces. There were no hearing difficulties and no history of vertigo. On admission the physical examination revealed generalized arteriosclerosis and a small, soft, tender mass over the right mastoid which appeared to be a neurofibroma. The neurologic examination revealed a horizontal nystagmus on looking toward the right, paralysis of the left vocal cord, absent left palatal and pharyngeal reflexes, atrophy of left sternomastoid and trapezius, atrophy of the left side of the tongue, asynergia and dysmetria on the left arm and leg, a positive Romberg and a questionable hypesthesia of the left side of the body. Operation: Oct. 30, 43. Unilateral cerebellar approach, left. Resection of the cerebellar cap. A rather large tumor was found involving particularly the floor of the posterior fossa and extending into the spinal canal through the foramen magnum. The VIIIth N. was not involved. The tumor was totally removed. Weight: 25.8 gms. Histological diagnosis: Neurinoma. Patient had a smooth and rapid convalescence. No hearing loss was detected after the operation. When seen a year later the patient was much improved.

Comments: Neurinomas of the XIth N. are very uncommon and when found they are usually accompanied by evidence of neurofibromatosis elsewhere in the body. In our case it apparently started in the spinal canal forcing its way into the posterior fossa via the foramen magnum. As in this case, neurinomas of this type do not represent diagnostic problems.

PATHIOLOGICAL CONSIDERATIONS

Voluminous literature has been written regarding the histogenesis and microscopic appearance of the neurinomas and we consider it superfluous to dwell on the controversial discussion of the subject, as the real origin of these tumors is still debatable. It suffices, then, to mention briefly the current views.

The most plausible explanation about the origin of these tumors is the one proposed originally by von Recklinghausen (28) who suggested their connective tissue origin, a view subsequently supported by Mallory (21), Penfield (27) and Tarlov (30). On the other hand their neuroectodermal origin in the Schwann cells, as advocated by Verocay (31) and later supported by Antoni (1), Masson (22) and Murray and Stout (23), also has its strong points. Cushing (5) took an intermediate view in considering them as a possible transition between neuroglia and connective tissue.

Almost everyone, however, has agreed on their histological appearance. These tumors are primarily composed of two kinds of tissue (12), the compact cellular mass (type A or fibrillar tissue of Antoni) and the loose-meshed tissue (type B or reticulated tissue of Antoni). Their general appearance is furthermore influenced by the age of the growth and subsequent degenerative changes.

That these tumors are morphologically like the peripheral neurofibromas of von Recklinghausen is a known fact. Their only differential point rests on the presence of nerve fibrils in the capsule in the former and in the center of the tumor in the latter. Penfield (26), nevertheless, has also made the remark that the cells in the neurofibromas are more mature, an observation that can hardly be corroborated.

As shown in the accompanying photomicrographs (Fig. 6), all the neurinomas at the angle are histologically the same regardless of their location and of whether or not there was evidence of peripheral neurofibromatosis elsewhere. The variations usually found in acoustic neurinomas are likewise found in the rest and hence a histological differentiation is impossible.

Grossly, however, the bilateral neurinomas and the neurinomas at the recess associated with multiple peripheral neurofibromas were

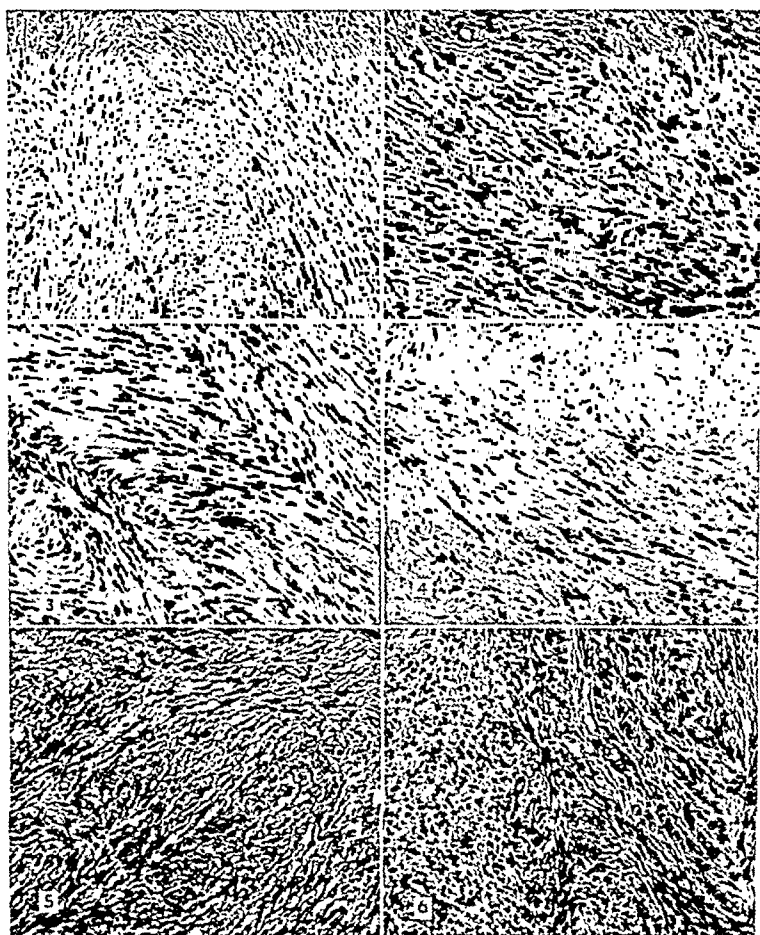


FIG. 6. Photomicrographs of different neurinomas at the cerebellopontile recess. Low power magnification. Hematoxylin and eosin.

1. Unilateral acoustic without peripheral neurofibromas (M. R. 300471)
2. Unilateral acoustic with peripheral neurofibromas (L. Y. 207209)
3. Bilateral acoustic (G. W. 335824)
4. Neurinoma of the Vth N (L. R. 261715)
5. Neurinoma of the Xth N (I. B. 237504)
6. Neurinoma of the XIth N (C. W. 305730)

found in our cases to be harder than the unilateral acoustic tumors, in spite of their similar histological appearance. Perhaps this may be

explained by the relative old age of the tumors in the former, if we recall their more prolonged duration of symptoms.

SUMMARY

1. An analysis of one hundred and sixty cases of neurinomas at the cerebellopontile recess has been presented.
2. Their incidence, location, symptoms, signs, operation, operative mortality and end results have been discussed.
3. Emphasis has been placed on the chronology and duration of symptoms, as well as on the average age at onset.

BIBLIOGRAPHY

1. ANTONIO, N. R. E.: *Über Rückenmarkstumoren und Neurofibroma.* München und Wiesbaden, 1920.
2. BÁRÁNY, R.: Die nervösen Störungen des Cochlear—und Vestibularapparates. Cf. v. Lwczandowski Handbuch der Neurologie, Berlin, 1910, 1: 919-958.
3. COTTERILL, J. M.: Remarks on the surgical aspects of a case of cerebellopontine tumor by Bruce. Tr. Med. Chir. Soc., Edinburgh, 1898-99, 18: 215.
4. CUSHING, H.: The establishment of cerebral hernia as a decompressive measure for inaccessible brain tumor, with the description of intermuscular methods of making a bone defect in temporal and occipital regions. Surg., Gynec., Obst., 1905, 1: 297-314.
5. CUSHING, H.: Tumors of the Nervus Acusticus and the Syndrome of the Cerebellopontile angle. Philadelphia and London, W. B. Saunders, 1917, 1-278.
6. DANDY, W. E.: An operation for the total extirpation of tumors of the cerebellopontine angle. A preliminary report. The Johns Hopkins Hosp. Bull., 1922, 33: 344-345.
7. DANDY, W. E.: An operation for the cure of tic douloureux. Partial section of the sensory root at the pons. Arch. Surg., 1929, 18: 687-734.
8. DANDY, W. E.: The treatment of trigeminal neuralgia by the cerebellar route. Ann. Surg., 1932, 96: 787-795.
9. DANDY, W. E.: Concerning the cause of trigeminal neuralgia. Am. Jour. Surg., 1934, 24: 447-455.
10. DANDY, W. E.: An operation for the total removal of cerebellopontine (acoustic) tumors. Surg., Gyn., Obst., 1925, 41: 129-148.
11. DANDY, W. E.: Removal of cerebellopontine (acoustic) tumors through a unilateral approach. Arch. Surg., 1934, 29: 337-344.
12. ELSBERG, C. A.: Surgical Diseases of the Spinal Cord, Membranes and Nerve Roots. New York, Paul B. Hoeber, Inc., 1941, 238-242.
13. FORD, F. R.: Diseases of the Nervous System in Infancy, Childhood and Adolescence. Springfield, Illinois, Charles C. Thomas, 1944. 2nd Ed., p. 146.

14. FRAZIER, C. H.: Remarks upon the surgical aspects of tumors of the cerebellum. *New York Med. Jour.*, 1905, **81**: 272-344.
15. GONZALEZ-REVILLA, A.: Tic douloureux and its relationship to tumors of the posterior fossa. Analysis of twenty-four cases. To be published in *Jour. Neurosurg.*
16. HANRAHAN, E. M., AND DANDY, W. E.: A procedure to correct facial paralysis. *Jour. Am. Med. Assoc.*, April 8, 1944, **124**: 1051-1053.
17. HARDY, M., AND CROWE, S. J.: Early asymptomatic acoustic tumors. *Arch. Surg.*, 1936, **32**: 292-301.
18. HENSCHEN, F.: Über Geschwülste der hinteren Schädelgrube, insbesondere des Kleinhirnbrückewinkels, 1910, Jena, Gustave Fisher.
19. JACKSON, J. H.: Selective Writings. London, Hodder and Stoughton, 1931.
20. KRAUSE, F.: Zur Freilegung der hinteren Felsenbeinfläche und des Kleinhirns. *Beitr. z. klin. Chir.*, 1903, **37**: 728-764.
21. MALLORY, F. B.: The type of cell of the so-called dural endothelioma. *Jour. Med. Research*, 1919, **41**: 349.
22. MASSON, P.: Experimental and spontaneous Schwannomas (peripheral gliomas). *Am. Jour. Path.*, 1932, **8**: 367-414.
23. MURRAY, M. R., AND STOUT, A. P.: Schwann cell versus fibroblast as the origin of the specific nerve sheath tumor. *Am. Jour. Path.*, 1940, **16**: 60.
24. NIELSEN, A.: Acoustic tumors with special reference to end results and sparing of the facial nerve. *Ann. Surg.*, 1942, **115**: 849-868.
25. OLSEN, A., AND HORRAX, G.: The symptomatology of acoustic tumors with special reference to atypical features. *Jour. Neurosurg.*, 1944, **1**: 371-378.
26. PENFIELD, W.: Encapsulated tumors of the nervous system. *Surg., Gyn., Obst.*, 1927, **45**: 178.
27. PENFIELD, W.: Cytology and Cellular Pathology of the Nervous System. New York, Paul B. Hoeber, 1932.
28. RECKLINGHAUSEN, F. VON: Über die multiplen Fibrome der Haut und ihre Beziehung zu den multiplen Neuomen. *Festschr. f. Virchow*, Berlin, 1882.
29. STONE, R. S., AND SCHULZE, F. J.: Ventricular changes caused by proved tumors of the brain. *Amer. Jour. Roentgenol.*, 1938, **39**: 523-533.
30. TARLOV, I. M.: Origin of the perineurial fibroblastoma. *Am. Jour. Path.*, 1940, **16**: 33-40.
31. VEROCAY, J.: Multiple Geschwülste als Systemerkrankung am nervösen Apparate. *Festschr. f. Chiari*, Wien und Leipzig, Braunmuller, 1908, p. 278-415.
32. WOLFF, H. G.: Headache mechanisms. A summary. *Research Publ. Assoc. for Research Nerv. and Ment. Dis.*, Williams and Wilkins, Baltimore, 1943, **23**: 176-177.
33. WOOLSEY, G., FRAENKEL, J., HUNT, J., AND ELSBERG, C.: Contribution to the surgery of neurofibroma of the acoustic nerve, with remarks on the surgical procedure. *Ann. Surg.*, 1904, **40**: 293-319.

PROCEEDINGS OF THE MEETINGS OF THE JOHNS HOPKINS MEDICAL SOCIETY

HELD IN HURD MEMORIAL HALL, DECEMBER 9, 1946

Symposium on Irradiation Therapy in Ophthalmology and Otolaryngology: I. General Considerations of Irradiation. DR. CURTIS F. BURNAM (*Department of Surgery, Johns Hopkins Hospital*).

At the present time, so far as therapy is concerned, only x-ray and radium need to be considered. There are a number of newer forms of irradiation which have proved of value but not in any of the pathological processes found in the nose, throat or eye.

A brief report is presented on the nature of roentgen and radium rays, how they are produced, and how they are measured. The importance of filters in changing the quality of irradiation is discussed for both x-ray and radium. Very briefly, the methods of separating radon from radium are considered. As the question often arises "Why use radium?", "Why use radon?", a discussion of the merits of each of these forms of applying gamma and beta rays is considered. An explanation of the meaning and methods of recording radium and radon dosages is presented. The physical changes that take place in a beam of irradiation in the human body are discussed, as well as the chemical and biological changes induced by the absorption of radium and x-rays. It is pointed out that the effects of different wave lengths are identical and that the effects of beta radiation are the same as those of gamma provided an equal quantity is absorbed in a tissue. Very briefly, methods of protecting the personnel using radium and x-ray are described. The importance of distance and of time of exposure, as well as of heavy screening, is explained. A brief description is given of the nasal applicator used in nose and throat work, particularly in treating lymphoid tissue in the nasopharynx, and of the beta ray applicator used in treating superficial eye conditions.

II. Irradiation of the Nasopharynx. DR. SAMUEL J. CROWE (*Department of Laryngology and Otolaryngology, Johns Hopkins Hospital*).

Many of the hearing disorders of adult life begin in childhood, and if we are to learn more about the causes, treatment, and prevention of deafness, we must concentrate our studies on children. Almost every type of middle and inner ear deafness seen in adults is found in children, with this important difference: in children, the impairment is just beginning and opportunities are offered for study of the life history of the disease and for developing some kind of effective and even preventive therapy.

A common cause of impaired hearing in children is frequent upper respiratory infections and hypertrophic lymphoid tissue in and around the pharyngeal orifices

of the Eustachian tubes. In aviators, submariners, and others who work under rapidly changing pressures, acute changes are brought about in the middle ear, due to colds and hypertrophied lymphoid tissue that interferes with the normal function of the Eustachian tubes. In both, the symptoms are due to aerotitis; abrupt and painful in aviators, painless and often asymptomatic in children until secondary changes in the middle ear begin to cause progressive loss of hearing.

Irradiation of the nasopharynx has been practiced in this hospital for nearly 20 years. It is a simple, safe, and inexpensive way to remove lymphoid tissue from locations inaccessible surgically. Thousands of patients have been treated, and many have been followed for 15 years. We are convinced this is a valuable public health measure. If school children from 8 to 10 years of age were examined with otoscope, nasopharyngoscope, tuning forks, voice and audiometer, and those with hypertrophic lymphoid tissue around the orifice of the Eustachian tubes irradiated, we think that disability from deafness later in life could be reduced as much as 50 per cent.

III. Beta Irradiation in Ophthalmology. DR. CHARLES E. ILIFF (*Department of Ophthalmology, Johns Hopkins Hospital*).

Beta rays possess the same qualities as other rays in the power of selective tissue destruction, but in contrast to gamma rays their penetration is shallow. In no single case has any damage to the lens been observed either clinically or experimentally.

Excellent results have been obtained in the treatment of vernal conjunctivitis. Recurrences are less frequent, and when these do occur are less severe.

In anterior ocular tuberculosis beta therapy seems to shorten the course and decrease the severity of the symptoms with less residual scarring of the cornea. Irradiation, though, did not prevent future tuberculous recurrences.

Small benign tumors of the lids and anterior segment can be removed easily and safely and give an excellent cosmetic result.

In corneal scars, where vascularization is a prominent feature and where there is still activity, irradiation appears beneficial. In old, calcified, and dense scars, treatment is not successful.

Superficial vascularization after keratectomy and keratoplasty can be controlled.

Encouraging results are obtained in the treatment of acne rosacea keratitis.

Dystrophies, sarcoid, lupus erythematosus, pemphigus, punctate keratitis, and corneal ulcers due to pyogenic infections, are not improved by beta rays and may be made worse by their use.

ON CERTAIN VASCULAR EFFECTS OF CURARE IN MAN: THE "HISTAMINE" REACTION¹

D. GROB, J. L. LILIENTHAL, JR. AND A. M. HARVEY

From the Physiological Division, Department of Medicine, The Johns Hopkins University and Hospital

Curare possesses in high degree the property of blocking the transmission of impulses across synaptic and neuromuscular junctions (8, 9). In recent years curare has been made available in a purified form which permits rigid pharmacological standardisation. As a result, curare has been employed widely for its lissive and paralysing effects to relax skeletal muscle in a variety of clinical applications, including surgical anaesthesia (18), endoscopy (2), convulsive shock therapy (6), convulsive disorders, particularly tetanus (43, 44), and spastic and dystonic states (10, 40).

However, the clinical application of the predominant action of curare on skeletal muscle has brought to light actions on other systems which have introduced certain limitations in the general use of curare. The following side-actions of curare and of its active principle, crystalline *d*-tubocurarine chloride, have been reported; the more serious of these have been infrequent and usually have occurred only after prolonged curarisation.

a) *Cardiovascular*—A transient fall in arterial blood pressure accompanied by a subjective feeling of warmth, giddiness and headache is a frequent occurrence following a single therapeutic dose of 50 to 100 units (13, 14, 25, 43). Occasionally the hypotension has been severe (12) and during prolonged curarisation shock with hemoconcentration has sometimes supervened (34). Similar reactions have been produced in experimental animals (19, 30, 35). The rapidity of administration of curare, as well as the dose, are important factors in the manifestation of its cardiovascular and other pharmacologic effects (19). The drug has been found to have no effect on the electrocardiogram of man (39) or animals (30).

b) *Respiratory*—The development of bronchospasm varying from

¹ Work done under a contract between the Office of Naval Research, U. S. Navy Department, and the Johns Hopkins University.

mild to fatal in degree has been reported in man and in animals (17, 43 to 47, 49).

c) *Secretory*—Excessive salivary and bronchial secretion has been noted following the administration of therapeutic doses to man (13, 14, 47) and in the experimental animal (46).

d) *Central Nervous System*—Smaller doses are frequently associated with slight drowsiness, confusion, or euphoria (20, 25), while large doses may result in depression of electroencephalographic activity (40) and unconsciousness (47). In the frog large doses may cause brain potentials to vanish (16, 36). However, recently a study of a human subject under profound curarisation revealed no alterations in the electroencephalogram, consciousness and sensorium (40a).

e) *Skin*—A few instances of urticaria have been noted following the administration of curare prior to metrazol shock (6).

Several experimental studies have established that the depression of neuromuscular conduction induced by curare may be lightened by eserine and neostigmine (3, 7), acetylcholine and epinephrine (38), potassium (48) and guanidine (24). But recently certain observations in man and animals (26, 34) have indicated that the use of neostigmine as an antidote to large doses of curare or *d*-tubocurarine has failed to prevent death, and that large doses of neostigmine may even increase the toxicity of sublethal doses of curare. Other observations have indicated that the cardiovascular and respiratory effects of curare may be lessened by epinephrine and ephedrine (25, 44, 47, 49), and that ephedrine may increase the antidotal value of small doses of neostigmine (26).

Recently Comroe and Dripps (11) have reported observations on the vascular effects of curare which parallel part of the study to be reported here. They offered the suggestion that these effects were due to the action of histamine and might be prevented by the newer anti-histamine agents.

The experiences of many investigators which have been summarised briefly above, together with the observation that the intra-arterial injection of curare produced extraordinary vascular changes in the injected area (21) indicated the necessity for investigation of the actions of curare other than those on neuromuscular mechanisms. This

communication reports a study of certain vascular effects of curare observed in human subjects.

METHODS

The following drugs were used in this study:

Curare (Intocostin, Squibb)-containing 20 units per ml. in aqueous solution with 0.5 per cent chlorobutanol as a preservative (pH 4.6). *d-Tubocurarine chloride*² (Squibb)—the crystalline active principle of curare in a concentration of 20 units per ml. (containing 2.7 mg. per ml., and equivalent to 20 units or 20 mg. of standard curare) in aqueous solution of 0.5 per cent chlorobutanol (pH 3.5). *Histamine phosphate*—Aqueous solutions containing 2 mg. and 0.125 mg. of histamine base per ml.. *Pyribenzamine*³ (Ciba)—Aqueous solutions containing 3 mg. and 10 mg. per ml.. *Benadryl*⁴ (Parke, Davis)—Aqueous solution containing 30 mg. per ml.. *Beta-crythroidine HCl*⁵ (Merck)—Aqueous solutions containing 50 mg. per ml. (pH 6.5) and 100 mg. per ml. (pH 6.0).

Injections of the drugs under study have been made intra-cutaneously, intravenously, intramuscularly and intra-arterially. The latter injections have been made into the brachial artery through an in-lying needle introduced through an area of local anesthesia (induced with a 0.5 per cent solution of procaine). Following intra-arterial injection a pneumatic cuff applied above the site of injection was inflated to a pressure of 100 mm. of Hg for two minutes to prolong localisation of the drug. The pneumatic cuff was then deflated slowly over a period of one to two minutes. On several occasions measurements of the volume of the forearm and hand were made by the displacement of water at body temperature in a calibrated cylinder.

In view of speculations regarding the role played by impurities

¹ Kindly furnished by Dr. H. S. Newcomer, E. R. Squibb and Co., New York.

² N'-Pyridyl-N'-benzyl-N-dimethylethylene diamine hydrochloride, kindly furnished by Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

³ B-Dimethylaminoethyl benzhydryl ether hydrochloride, kindly furnished by Parke, Davis and Co., Detroit, Michigan.

⁴ Kindly furnished by Merck and Co., Inc., Rahway, New Jersey.

present in preparations of curare (45) it may be noted here that in this study the reactions following curare have been indistinguishable, both qualitatively and quantitatively, from those produced by its crystalline active principle, *d*-tubocurarine chloride.

RESULTS

Intracutaneous Administration

The intracutaneous administration of 0.05 ml. of curare or of *d*-tubocurarine solution (containing 1 mg. of curare or 0.135 mg. of crystalline *d*-tubocurarine chloride) into the flexor surface of the forearm of 34 normal subjects resulted in every case in a wheal and flare at the site of the injection with small pseudopodal extensions of the wheal in most cases (Figure 1). The local reaction reached its maximal intensity in five to ten minutes, began to diminish 30 minutes later and disappeared within two to three hours after the injection. The average diameter of the flare at the height of the reaction was 65 mm., of the wheal 20 mm., and the average length of the pseudopodal extensions of the wheal was 9 mm. The subjects reported a transient burning sensation at the site of the injection, sometimes followed by itching.

Intra-arterial Administration

Fifteen to 50 units of curare and of *d*-tubocurarine were administered intra-arterially to 27 normal subjects.

The intra-arterial injection of curare and of *d*-tubocurarine produced identical effects which were proportional to the amount of drug. Immediately following the injection there was a transient burning sensation which extended down the forearm into the hand and fingers. Within one or two minutes after the injection there was marked loss of strength or complete paralysis of all the muscles of the injected forearm and hand. Motor power returned slowly during the next two hours. When the blood pressure cuff was deflated (two minutes after the injection) the injected forearm immediately became intensely hyperemic and engorged and within two minutes after release of the cuff there appeared over the forearm and hand numerous areas of blue and purple discoloration, which did not blanch

on pressure and which resembled ecchymoses (Figure 2). These discolored areas faded gradually and then vanished during the next 30 minutes. As the discoloration diminished the injected forearm and hand gradually swelled with the appearance of a diffuse, firm edema which did not pit on pressure, and with the development of broad



FIG. 1. Right forearm: The response to the intracutaneous injection of 0.05 ml. of curare. Left forearm: The upper wheal represents the site of intracutaneous injection of 0.05 ml. curare after pyribenzamine (see text). The lower wheal is the site of injection of pyribenzamine alone.

wheals over the anterior surface of the forearm. The swelling and wheals were visible 15 minutes after the injection and were maximal 15 minutes later. The wheals were accompanied by a slight sensation of itching. The increase in the volume of the injected forearm and hand varied from 10 to 20 per cent. Where the skin was swollen and

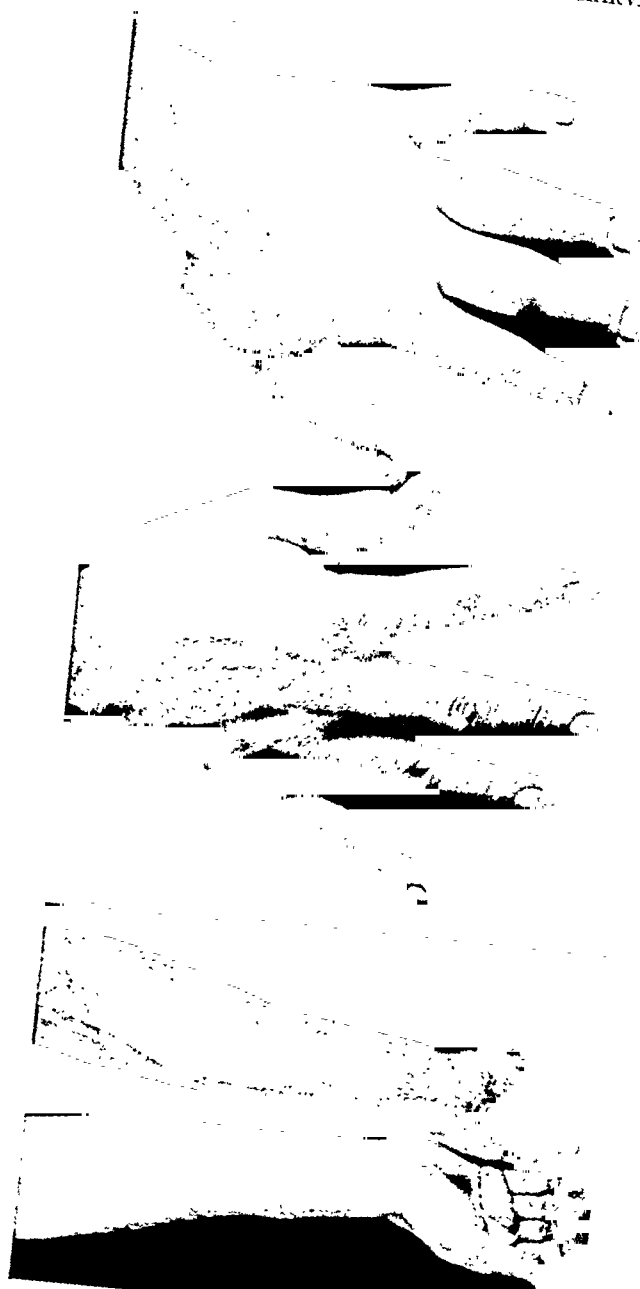


FIG. 2. INJECTION OF 50 UNITS OF *d*-TUBOCURARINE INTO LEFT BRACHIAL ARTERY

Left: five minutes after injection, showing discoloration. Right: 30 minutes after injection, showing edema of hand.

tight, as in the hand, there was some blanching, and in these areas there was also slight hypalgesia to pin prick.

These visible changes were localised to the injected hand and forearm, distal to the point of injection. The wheals gradually diminished and disappeared within a few hours. The swelling persisted for a longer period of time, which was proportional to the amount of drug that had been injected. Following the administration of 30 units of curare or *d*-tubocurarine the swelling was completely gone within 16 hours, and, following 50 units, within 36 hours.

The visible changes in the injected arm were accompanied by evidence of marked vasodilatation, occurring first in the injected forearm and hand and then generally. This was indicated by virtual arterialisation of the venous blood returning from both forearms, as reflected by the blood gas contents (Figure 3). Peripheral vasodilatation was also indicated by the progressive rise in the skin temperature of both upper extremities (measured in a cold room by means of skin thermocouples) from a pre-injection temperature of about 20°C. to a maximum of 32°C. (Figure 4). The skin temperature rose a little more rapidly and to a slightly higher level in the injected arm than in the opposite arm, and the initial vasodilatation was frequently followed by some evidence of transient vasoconstriction (Figures 4 and 6), which may have been compensatory in nature. Further evidence of generalised vasodilatation was furnished by the subjective feeling of warmth, giddiness and frontal headache, which were experienced following release of the blood pressure cuff, and by a transient fall in blood pressure which averaged 20 mm. of mercury systolic and 10 mm. diastolic.

When the curare or *d*-tubocurarine was injected intra-arterially without temporarily obstructing the venous return proximal to the site of injection the neuromuscular and local and general vascular effects of the drug were significantly reduced in degree and in duration. The application of a blood pressure cuff alone for two minutes, without intra-arterial injection of the drug, did not produce any of the effects described above.

Intravenous and Intramuscular Administration

The injection of 15 to 50 units of curare or of *d*-tubocurarine intravenously (at the rate of 25 units a minute) and intramuscularly re-

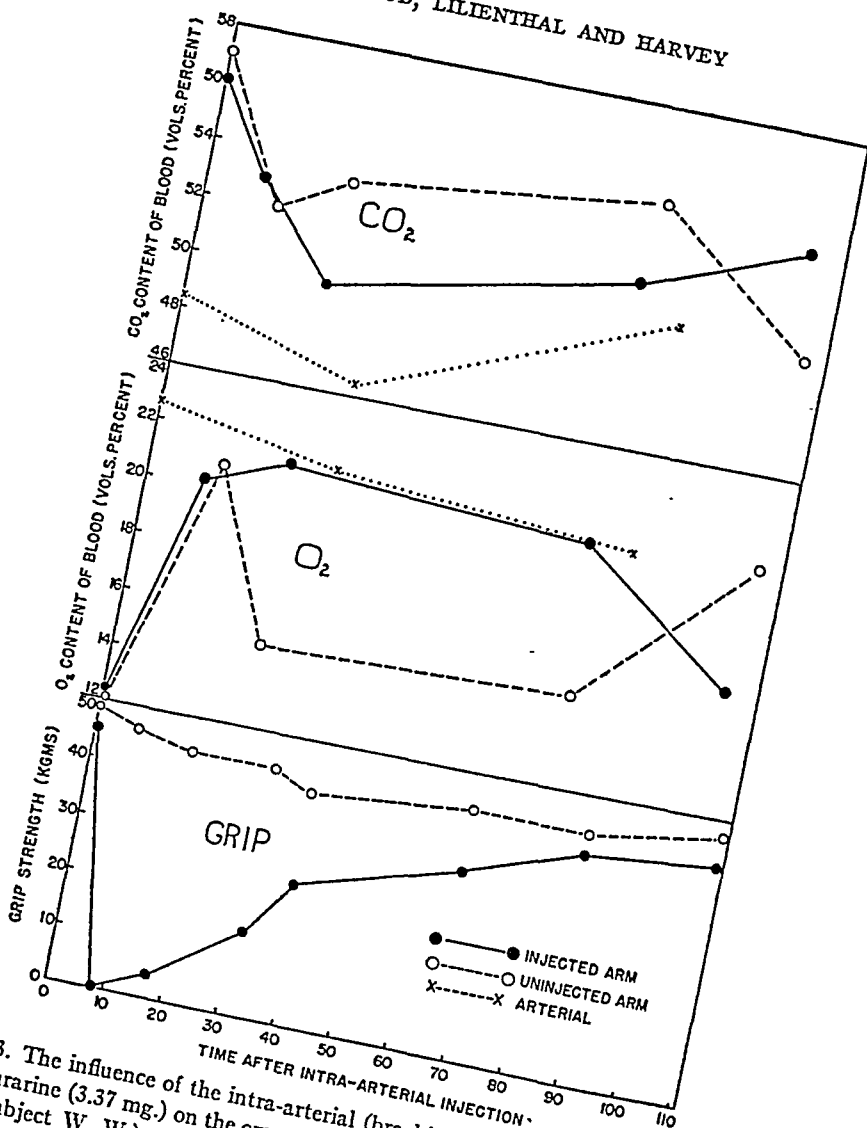


FIG. 3. The influence of the intra-arterial (brachial) administration of 25 units of tubocurarine (3.37 mg.) on the oxygen and carbon dioxide content of the venous blood (Subject W. W.)

● — Venous blood from the injected arm.
 ○ - - - Venous blood from the opposite arm.
 x ····· Arterial blood from the injected arm.
 ● — Grip strengths of the hands are recorded below, with the solid line representing the injected arm.

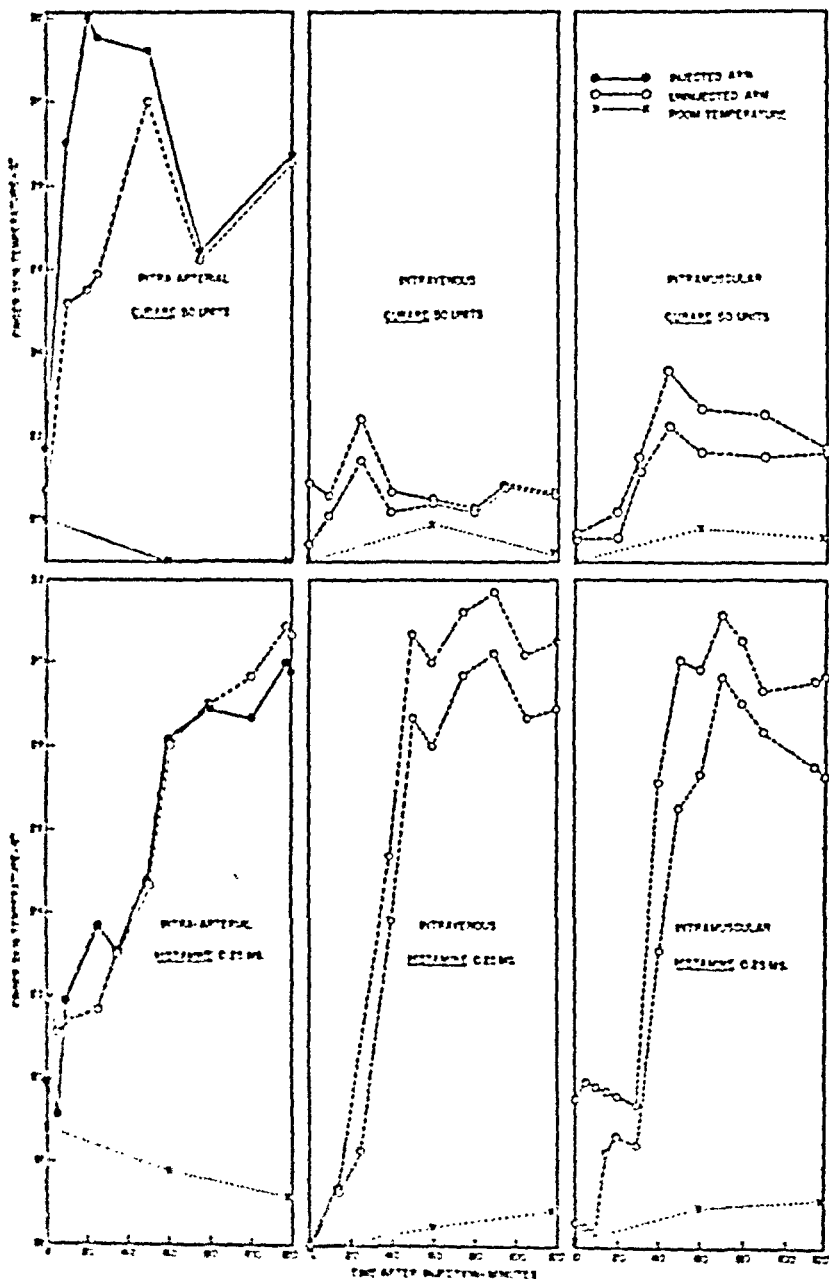


FIG. 4. Comparison between the influence of curare and histamine on finger skin temperature when administered intra-arterially, intravenously, and intramuscularly. (Subject E. T.)

- — ● Skin temperature of injected arm.
- - - - ○ Skin temperature of uninjected arm.
- x x Room temperature

sulted in much less marked vascular effects than did intra-arterial injection (Figure 4). There was no discoloration of the skin, wheal formation, or detectable edema. The rise in skin temperature was a little more pronounced and longer sustained following intramuscular administration of the drug than after its slow intravenous injection.

None of the vascular or neuromuscular effects of curare and *d*-tubocurarine were reproduced by the intra-arterial administration of up to 3 ml. of normal saline or of 0.5 per cent chlorobutanol (pH 4.5), the preservative which was present in the preparations that were used. The intracutaneous administration to 10 normal subjects of 0.05 ml. of 0.5 per cent chlorobutanol did produce a slight flare (average diameter 12 mm., maximum 20 mm.), but no wheal or pseudopods.

Comparison with the Vascular Effects of Histamine

The reported occurrence of hypotension, hemoconcentration, and bronchoconstriction following the administration of curare and *d*-tubocurarine, and the vascular effects of these drugs which have been described above, may be compared with the effects of histamine, an agent which in sufficient concentration produces vasodepression, bronchoconstriction, and capillary damage.

The local wheal and flare and sensation of burning and itching produced by 0.05 ml. of curare or *d*-tubocurarine solution was the same as that produced by 0.05 ml. of histamine solution containing 2 mg. of histamine base per ml. However, the pseudopods produced by histamine were two to three times longer than those produced by curare and *d*-tubocurarine, and the generalised vasodilatation and headache that occasionally followed intracutaneous histamine was never observed after the intracutaneous administration of curare or *d*-tubocurarine. It is of interest that the sensitivity of different subjects to the local effect of curare or *d*-tubocurarine paralleled in general their sensitivity to histamine. One subject with diabetic peripheral neuritis and evidence of partial sympathetic and sensory denervation of his forearms showed no wheal or flare following the intracutaneous injection of histamine in the involved area, and absence of wheal, with a slight flare, following the intracutaneous injection of curare or of chlorobutanol.

The intra-arterial injection of 0.25 mg. of histamine base into the brachial artery produced a transient burning sensation, intense

flushing, transient ecchymotic discoloration, diffuse swelling (41), and slight wheal formation in the injected arm, distal to the point of injection. This was accompanied by evidence of marked vasodilatation, occurring first in the injected arm and then generally, as manifested by a progressive rise in the skin temperature of the upper extremities (Figure 4), by subjective warmth, giddiness, frontal headache, and transient hypotension. The only observed differences between the effects of intra-arterial curare and histamine were the absence of any change in the strength of the injected arm following the administration of histamine, and the somewhat greater systemic effect of the histamine, as manifested by greater subjective warmth, giddiness, headache, and hypotension.

The main difference between the general vascular effects of histamine and of curare was in the greater effectiveness of the intravenous and intramuscular administration of histamine as compared to curare. The administration of curare by these routes produced a much smaller rise in the skin temperature of the upper extremities than did the intra-arterial administration. In contrast, the effect of histamine was approximately the same by any of these routes (Figure 4) (5).

Because of the general similarity between the vascular effects of curare or *d*-tubocurarine, and of histamine, a study was made of the effect of these drugs, administered by various routes, on the secretion of acid by the stomach. The administration of 0.25 mg. of histamine produced approximately the same increase in the secretion of gastric acid, whether injected intra-arterially, intravenously or intramuscularly. On the other hand, while *d*-tubocurarine produced a marked increase in the secretion of gastric acid when administered intra-arterially, it caused only a moderate increase following intramuscular administration, and very little following intravenous administration (Figure 5).

Inhibition of the Vascular Effects of Curare and d-Tubocurarine by Antihistamine Drugs

Pyribenzamine and benadryl, which have been shown to be potent inhibitors of most of the pharmacological effects of histamine (29, 50), were administered in an attempt to block the vascular response to curare.

The intravenous administration of 0.05 g. of pyribenzamine

(3 mg. per ml.), prior to the injection of 0.05 ml. of curare or *d*-tubocurarine (20 units per ml.) into the same site, inhibited the wheal and most of the flare produced by the latter preparations (Figure 1). A similar inhibition was produced by benadryl, but a higher concentration (30 mg. per ml.) was required. The inhibitory effect of pyribenzamine and benadryl also could be demonstrated by mixing these drugs with the curare or *d*-tubocurarine prior to the injection. These amounts of pyribenzamine and benadryl injected intracutane-

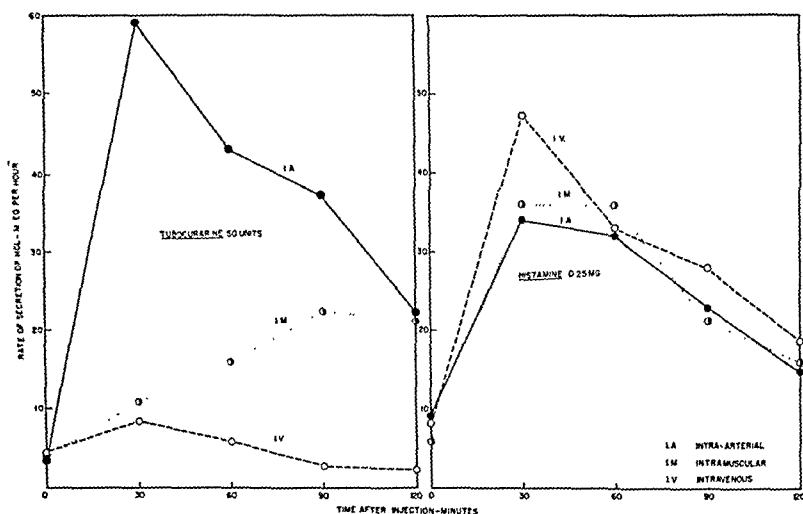


FIG. 5. Comparison between the influence of tubocurarine and histamine on the secretion of gastric acid when administered intra-arterially (●—●), intravenously (○- - -○), and intramuscularly (●.....●). Subject A. G.)

ously had a moderate but less completely inhibitory effect on the wheal and flare produced by 0.1 mg. of histamine base. The oral administration of pyribenzamine or benadryl (200 mg. 100 minutes and again 30 minutes before injection) had a much less markedly inhibitory effect on the wheal and flare produced by intracutaneous curare or histamine than did the local administration. However, measurements demonstrated a reduction in the size of the wheal, flare, and pseudopods produced by each drug, by as much as 40 per cent, and a more rapid disappearance of these local effects.

Pyribenzamine exhibited a markedly inhibitory action on the vascular effects of intra-arterial curare. The intra-arterial injection of 10 mg. of pyribenzamine produced intense pain and a transient, dark red flush in the injected arm. Fifty units of curare were then injected intra-arterially, and the proximal blood pressure cuff released two minutes later. The resulting weakness in the injected arm followed the usual time course (Figure 7) indicating that the injection had been complete. However, the hyperemia, venous engorgement, and ecchymotic discoloration that followed were considerably diminished and there were no wheals and almost no swelling of the injected arm and hand (Figure 6). Likewise, the usual increase in the skin temperature was almost completely inhibited in the injected arm and moderately inhibited in the opposite arm (Figure 7). The same results were obtained by mixing pyribenzamine with curare, in the amounts indicated above, prior to intra-arterial administration. A control injection of 10 mg. of pyribenzamine alone into the brachial artery had no significant effect on the strength or temperature of the extremities (Figure 8).

A similar inhibition of the local swelling, and local and general skin temperature changes produced by the intra-arterial administration of curare occurred following the oral administration of 200 mg. of pyribenzamine 100 and 30 minutes before the injection of 50 units of curare (Figure 7). The oral administration of pyribenzamine alone had no significant effect on the strength or temperature of the extremities (Figure 8).

Absence of Influence of Atropine and Neostigmine on the Vascular Effects of Curare

The wheal and flare produced by the intracutaneous administration of 0.05 ml. of curare (or *d*-tubocurarine) containing 20 units per ml. was not inhibited by the prior injection of 0.05 ml. of atropine sulfate (1.2 mg. per ml.) or neostigmine methylsulfate (0.5 mg. per ml.) into the same site.

Likewise the discoloration, swelling, and wheal formation of the injected arm, and the evidence of peripheral vasodilatation that followed the intra-arterial administration of 50 units of curare were unaffected by the prior intra-arterial administration of 1.2 mg. of atropine

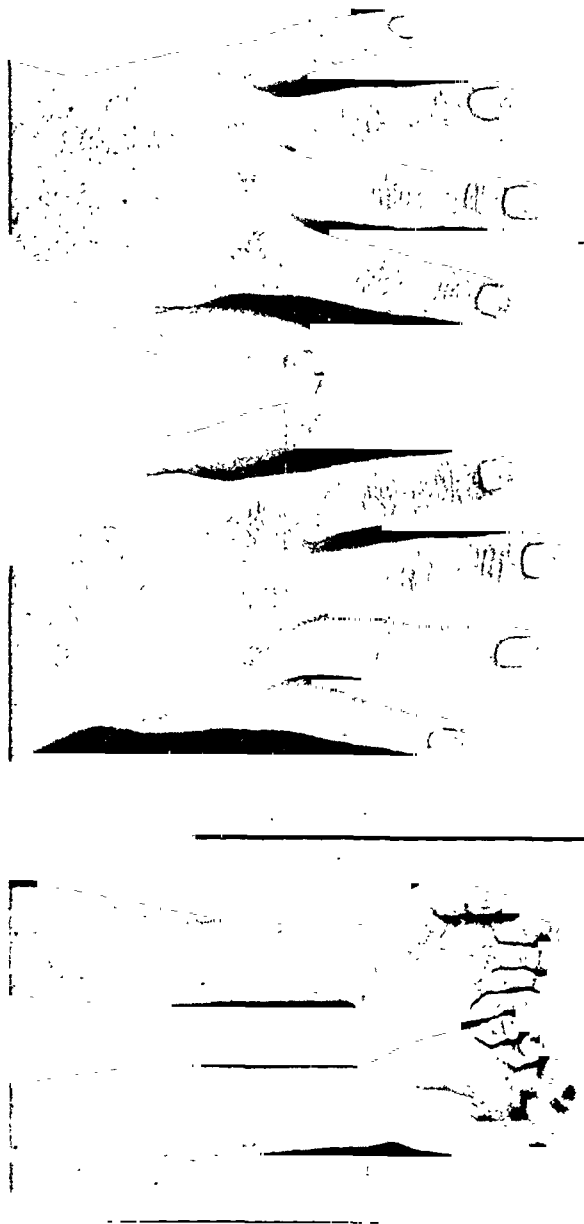


FIG. 6. INJECTION OF 10 MG. PYRIBENZAMINE FOLLOWED BY 50 UNITS OF CURARE INTO THE LEFT BRACHIAL ARTERY. Compare with Fig. 2

sulfate or 1.5 mg. of neostigmine methylsulfate (Figure 8). The neostigmine did inhibit to some degree the muscular weakness caused by the curare (Figure 8). Identical results were obtained by mixing atropine or neostigmine with curare before intra-arterial administra-

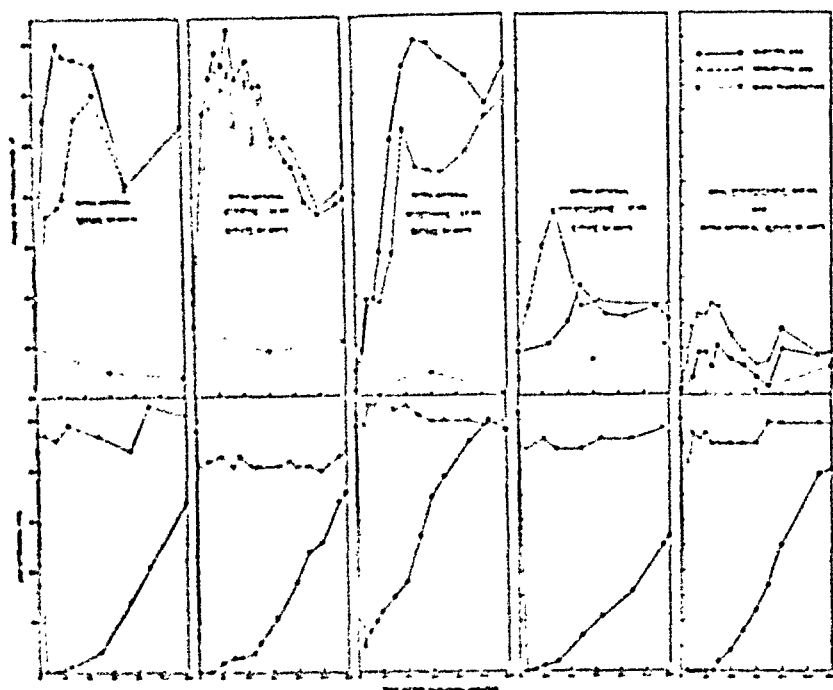


FIG. 7. The influence of 50 units of curare (50 mg.) administered intra-arterially on forearm skin temperature and grip strength, and the effect of previously administered atropine (1.2 mg.), neostigmine (1.5 mg.), and pyridostigmine (10 mg.) administered intra-arterially, and pyridostigmine (200 mg., 100 and 50 minutes before injection) administered orally. (Subject E. T.)

- — — — ● Injected arm.
- — — — ○ Uninjected arm.
- × × Room temperature.

tion. The intra-arterial administration of 1.2 mg. of atropine alone had no significant effect on the strength or temperature of the upper extremities (Figure 8) while the intra-arterial injection of 1.5 mg. of neostigmine alone caused immediate weakness, marked sweating,

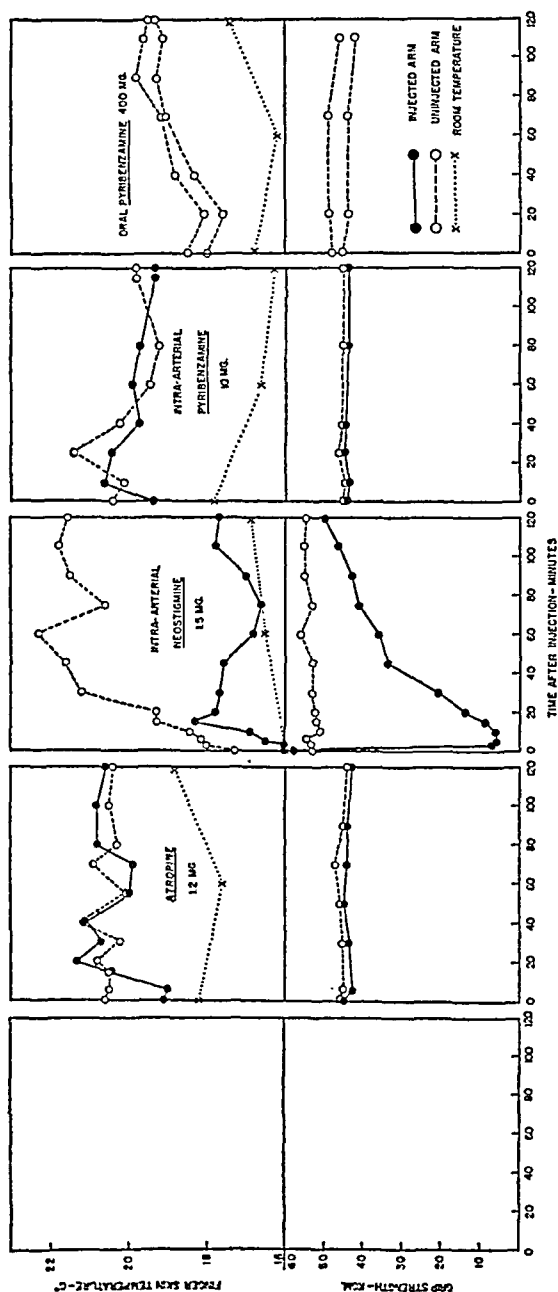


FIG. 8. (Control to Figure 7). The effect of the intra-arterial administration of atropine (1.2 mg.), neostigmine (15 mg.) and pyribenzamine (10 mg.), and the oral administration of pyribenzamine (200 mg. 100 and 30 minutes before), on finger skin temperature and grip strength. (Subject E. T.).

● —●—● Injected arm.
 ○ - - - ○ Uninjected arm.
 X X Room temperature.

and fasciculations in the injected arm. This was accompanied by a moderate increase in the skin temperature of the upper extremities (Figure 8), and a moderate increase in the oxygen content and decrease in carbon dioxide content of the venous blood of the upper extremities. This evidence of peripheral vasodilatation was less marked in the injected arm than in the opposite arm, perhaps due in part to the cooling effect of the marked sweating of the injected arm.

The Vascular and Central Nervous System Effects of Beta-Erythroldine

Beta-erythroldine is a tertiary ammonium base which, while structurally dissimilar to *d*-tubocurarine, has a similar effect on neuromuscular function (42) and has been used by a few investigators to promote muscular relaxation in shock therapy (12), tetanus (15), and spastic and dystonic states (10). The intravenous administration of a therapeutic dose of beta-erythroldine (300 mg., which is equivalent in neuromuscular effect to about 50 units of curare) has been reported to cause a transient fall in blood pressure (15, 37), rarely shock (12), and occasionally central nervous system symptoms, including drowsiness, confusion, and disorientation (25).

Study of the effects of beta-erythroldine hydrochloride administered intracutaneously to 10 subjects (5 mg. in 0.1 ml. at pH 6.5) and intra-arterially to three subjects (300 mg. in 3 ml. at pH 6.0) revealed vascular and neuromuscular changes similar to those described for curare (and *d*-tubocurarine), except that the degree of cyanosis, wheel formation, and evidence of local and general vasodilatation that followed intra-arterial administration were less than half as great as that observed after curare or tubocurarine (50 units). The central nervous system effects of beta-erythroldine, however, were much more marked than those mild symptoms which followed the intravenous administration of 60 units of curare.

The intra-arterial or intravenous administration of 150 to 300 mg. (five to 20 mg./kg.) of beta-erythroldine to eight normal subjects at the rate of 15 to 20 mg./minute resulted in drowsiness and apprehension in all of the subjects, conjunctival and scleral yellow and brown discoloration, cyanosis, impairment of memory, and feelings of unusual tension, restlessness, tachycardia, exaggerated tremors, and intermittent sternocostal and epigastric pain. These symptoms persisted

for as long as four hours, and were accompanied by electroencephalographic changes of varying degree in five of the six subjects who were so studied. These consisted of the intermittent appearance of bursts of slow waves (3 to 6 per second) of elevated voltage in all five, usually most marked in the frontal leads and increased by hyperventilation, increase in the potential and frequency of the electrical pattern in four subjects, and increased irregularity in three. In general, the electroencephalographic changes paralleled the severity of the central nervous system symptoms. The intravenous administration of atropine sulfate (1.2 mg.) or neostigmine methylsulfate (1.5 mg.) had no effect on the central nervous system symptoms or electroencephalographic changes.

DISCUSSION

The most prominent and best known pharmacologic action of curare is its ability to relax and paralyze skeletal muscle by inhibiting the transmission of impulses across the neuromuscular junction (8). Other less prominent pharmacologic effects of curare include its ability to produce hypotension, bronchoconstriction, excessive salivation and bronchosecretion, and, in overdose, hemoconcentration, shock, and depression of the central nervous system. Since these effects are produced by crystalline *d*-tubocurarine, as well as by the more commonly used preparations of curare, they appear to be pharmacologic effects of the drug itself and not due to the presence of impurities.

The vascular effects of curare were not inhibited by atropine, which prevents the muscarinic effects of acetylcholine. The swelling and wheal formation that occurred after intra-arterial curare could not be duplicated by the intra-arterial injection of atropine or neostigmine, nor have such effects been observed after intra-arterial acetylcholine (22) or adrenaline (23, 33). These observations, and the absence of significant anticholinesterase activity of *d*-tubocurarine (31) make it seem unlikely that the vascular effects of curare are cholinergic or adrenergic in origin. *d*-Tubocurarine has been reported to increase the rate of loss of potassium ions from isolated muscle (32), but Pearlstein and Weinglass (35) could detect no change in the serum potassium of dogs dying after prolonged curarisation. Preliminary observations of the effects of the intra-arterial administration of potassium chloride revealed that this compound produces severe local pain, but no

swelling or wheals comparable to that produced by curare or histamine (28).

Histamine produced local and systemic vascular effects (as well as increased secretion of gastric acid) which closely resembled the effects of intra-arterial curare. These findings suggest that the intra-arterial administration of curare may cause the release of a histamine-like substance which produces local edema and wheal formation, local and then general vasodilatation, and increased secretion of gastric acid. This substance apparently also may be released following the administration of curare intracutaneously, and to a lesser degree following intravenous and intramuscular injection.

The differences in degrees of histamine-like effects which followed the administration of curare by various routes suggest that the release of a histamine-like substance depends upon the attainment of a critical concentration of curare in certain tissues. An example of this indirect phenomenon is found in the report of West (46) who noted that the parenteral injection of curarine into intact guinea pigs produced bronchoconstriction, while contraction in the isolated bronchus occurred only after prolonged exposure to much higher concentrations of curarine.

Further evidence that the vascular effects of curare may be mediated by a histamine-like substance is provided by the inhibition of the vascular effects, both locally and systemically, by the antihistamine drug, pyribenzamine. Finally, Alam and his coworkers (4) have provided evidence for the release from skeletal muscle of histamine-like substances following the administration of curare. These observers reported that the injection of curare into an artery supplying the limb muscles of dogs caused the liberation into the circulation of a detectable amount of a substance which behaved chemically and biologically like histamine, and which was inactivated by histaminase. This substance was also released after the rapid intravenous administration of curare, and was accompanied by a measurable decrease in the existing store of histamine-like substances in the skeletal muscles, which they believed to be the chief source of the substance liberated into the circulation. This phenomenon was also observed after denervation, and therefore was not thought to be dependent on the paralyzing action of curare.

The mechanism for the release of a histamine-like substance after

the administration of curare and of beta-erythroidine remains unknown. Neither *d*-tubocurarine nor beta-erythroidine contains a moiety chemically related to histamine which might serve as a possible source. Histamine-like substances have been extracted from all tissues (1) and their release has been postulated in many other situations, such as allergy, anaphylaxis, and peptone shock, but the mechanism of release has not been elucidated. The wide range of chemical and physical agents that are capable of causing a local wheal and flare (27) emphasises further that the release of histamine-like substances may be a very general phenomenon.

The clinical significance of these observations lies in the reported occurrence during curarisation, especially if prolonged, of vascular and other phenomena which resemble the effects of histamine. The inhibition of such effects by the antihistamine drug, pyribenzamine, without affecting the neuromuscular action of curare, suggests that pyribenzamine may prove to be of value in the prevention and treatment of these histamine-like actions of curare. It is of interest that the vascular effects of curare were not inhibited by neostigmine; in fact, neostigmine itself produced evidence of local and general vasodilatation, which might potentiate the vascular effects of curare. This finding is of clinical significance, since, although neostigmine is capable of counteracting the neuromuscular effects of curare, it has been found to be ineffective or even harmful when used as an antidote to large doses of curare.

We are greatly indebted to Dr. Orthello R. Langworthy, Department of Psychiatry, who recorded and interpreted the electroencephalographic studies that have been described. Miss Sylvia Beck assisted in the skin temperature studies.

SUMMARY

1. Intracutaneous administration of curare and of *d*-tubocurarine chloride to human subjects produced a local flare and wheal with pseudopods. Intra-arterial administration produced weakness, discoloration, swelling, and wheals of the injected forearm and hand, evidence of local and general vasodilatation, and increased secretion

of gastric acid. Intravenous and intramuscular administration produced no evident swelling or wheals, and less peripheral vasodilatation and secretion of gastric acid.

2. The vascular effects of curare were not inhibited by the prior or simultaneous administration of atropine or of neostigmine.

3. The intracutaneous and intra-arterial administration of histamine produced vascular effects very similar to those of curare. The main difference between the vascular effects of histamine and of curare was in the greater effectiveness of the intravenous and intramuscular administration of histamine in the production of peripheral vasodilatation and increased secretion of gastric acid.

4. The local and general vascular effects of curare were inhibited by the prior or simultaneous administration of the antihistamine drug, pyribenzamine.

5. Beta-erythroidine, a depressant of neuromuscular conduction chemically dissimilar to curare, produced similar but less marked vascular effects. It also produced, in contrast to equivalent doses of curare, moderate central nervous system symptoms and electroencephalographic changes.

6. The vascular effects of curare suggest that the intra-arterial administration of this drug causes the release of a histamine-like substance which acts first locally, and then systemically. This substance apparently also is released after intracutaneous administration, and to a lesser degree after intramuscular and slow intravenous injection.

7. The release of a histamine-like substance following the administration of curare may explain the reported occurrence during curarisation of vascular and other phenomena which resemble the effects of histamine. Pyribenzamine may prove to be of value in the prevention and treatment of these histamine-like actions of curare.

REFERENCES

1. ABEL, J. J. AND KUBOTA, S. On the presence of histamine in the tissues of the body and among the hydrolytic decomposition products of proteins. *J. Pharmacol.*, 1919, 13: 243.
2. ADAMS, R. C. Curare as an aid to relaxation in anaesthesia. *Surg. Clin. North America*, 1945, 25: 735.
3. AESCHLIMANN, J. A. AND REINERT, M. Pharmacological action of some analogues of physostigmine. *J. Pharmacol.*, 1931, 43: 413.

4. ALAM, M., ANREP, G. V., BARSOUM, G. S., TALAAT, M., AND WEININGER, E. Liberation of histamine from the skeletal muscle by curare. *J. Physiol.*, 1939, 95: 148.
5. ALLEN, E. V. AND CRISLER, G. R. The results of intra-arterial injection of vasodilating drugs on the circulation. *J. Clin. Invest.*, 1937, 16: 649.
6. BENNETT, A. E. Preventing traumatic complications in convulsive shock therapy by curare. *J. Am. Med. Ass.*, 1940, 114: 322.
7. BRISCOE, G. Antagonism between curarine and prostigmine and its relation to myasthenia gravis. *Lancet*, 1936, 1: 469.
8. BROWN, G. L. Effect of small doses of curarine on neuromuscular conduction. *J. Physiol.*, 1938, 92: 23P.
9. BROWN, G. L. AND FELDBERG, W. Differential paralysis of the superior cervical ganglion. *J. Physiol.*, 1935, 86: 10P.
10. BURMAN, M. S. Therapeutic use of curare and erythroidine hydrochloride for spastic and dystonic states. *Arch. Neurol. Psychiat.*, 1939, 41: 307.
11. COMROE, J. H., JR., AND DRIPPS, R. D. The histamine-like action of curare and tubocurarine injected intracutaneously and intra-arterially in man. *Anesthesiology*, 1946, 7: 260.
12. CLECKLEY, H., HAMILTON, W. P., WOODBURY, R. A., AND VOLPITTO, P. P. Blood pressure studies in patients undergoing convulsive therapy. *South. M. J.*, 1942, 35: 375.
13. CULLEN, S. C. The use of curare for the improvement of abdominal muscle relaxation during inhalation anaesthesia. *Surgery*, 1943, 14: 261.
14. CULLEN, S. C. Clinical and laboratory observations on the use of curare during inhalation anaesthesia. *Anesthesiology*, 1944, 5: 166.
15. CULLEN, S. C., AND QUINN, C. S. The use of curare in the treatment of tetanus. *Surgery*, 1943, 14: 256.
16. FEITELBERG, S., AND PICK, E. P. Action of curare on the brain of the frog. *Proc. Soc. Exp. Biol. Med.*, 1942, 49: 654.
17. GRIFFITH, H. R. Curare as an aid to the anaesthetist. *Lancet*, 1945, 2: 74.
18. GRIFFITH, H. R., AND JOHNSON, G. E. The use of curare in general anaesthesia. *Anesthesiology*, 1942, 3: 418.
19. GROSS, E. G., AND CULLEN, S. C. The action of curare on the smooth muscle of the small intestine and on the blood pressure. *Anesthesiology*, 1945, 6: 231.
20. HARRIS, M. M., PACELLA, B. L., AND HORWITZ, W. A. A study of the use of curare in metrazol convulsant therapy with some electroencephalographic observations. *Psych. Quart.*, 1941, 15: 537.
21. HARVEY, A. M., LILIENTHAL, J. L., JR., GROB, D., AND JONES, B. F. The administration of di-isopropyl fluorophosphate (DFP) to man, IV. *Bull. Johns Hopkins Hosp.*, in press.
22. HARVEY, A. M., LILIENTHAL, J. L., JR., AND TALBOT, S. A. On the effects of the intra-arterial injection of acetylcholine and prostigmine in normal man. *Bull. Johns Hopkins Hosp.*, 1941, 69: 529.

23. HARVEY, A. M., AND LILIENTHAL, J. L. JR. Observations on the nature of tetany. The effect of adrenaline. Bull. Johns Hopkins Hosp., 1942, 71: 163.
24. HARVEY, A. M., AND MASLAND, R. L. The electromyograms in myasthenia gravis. Bull. Johns Hopkins Hosp., 1941, 69: 1.
25. HARVEY, A. M., AND MASLAND, R. L. Actions of curarizing preparations in the human. J. Pharmacol., 1941, 73: 304.
26. KOPPANYI, T., AND VIVINO, A. E. Prevention and treatment of *d*-tubocurarine poisoning. Science, 1944, 100: 474.
27. LEWIS, T. The blood vessels of the skin and their responses. London, Shaw and Sons, Ltd., 1927.
28. LILIENTHAL, J. L., JR. 1941, unpublished observations.
29. LOEW, E. R., MACMILLAN, R., AND KAISER, M. E. The anti-histamine properties of benadryl. J. Pharmacol., 1946, 86: 229.
30. MAUTNER, H., AND LUISADA, A. Antagonistic effect of asphyxia to curare paralysis of the vagus nerve. J. Pharmacol., 1941, 72: 386.
31. MCINTYRE, A. R., AND KING, R. E. *d*-Tubocurarine chloride and cholinesterase. Science, 1943, 97: 69.
32. MCINTYRE, A. R., AND KING, R. E. Influence of *d*-tubocurarine chloride on the liberation of potassium from frog skeletal muscle. Federation Proc., 1944, 3: 81.
33. MEYERSON, A., LOMAN, J., RINKEL, M., AND LESSES, M. F. Effects of the intra-arterial injection of acetylcholine, acetyl-beta-methylcholine chloride, epinephrine, and benzedrine sulfate. Am. Heart J., 1938, 16: 329.
34. NEWCOMER, H. S. Personal communication, 1947.
35. PEARLSTEIN, M. A., AND WEINGLASS, A. Fatal effects of prolonged complete curarization. Am. J. Dis. Child., 1944, 67: 360.
36. PICK, E. P., AND UNNA, K. The effect of curare and curare-like substances on the central nervous system. J. Pharmacol., 1945, 83: 59.
37. ROSEN, S. R., AND BORENSTEIN, M. V. Psychophysiological action of beta-erythroidine hydrochloride. Psych. Quart., 1941, 15: 163.
38. ROSENBLUTH, A., LINDSLEY, D. B., AND MORISON, R. S. Study of some decuricising substances. Amer. J. Physiol., 1936, 115: 53.
39. RUSKIN, A., EWALT, J., AND DECHERD, G. The electrocardiogram of curarised human patients. Dis. Nerv. Syst., 1943, 11: 2.
40. SCHLESINGER, E. B. Curare, a review of its therapeutic effects and their physiological bases. Amer. J. Med., 1946, 1: 518.
- 40a. SMITH, S. M., BROWN, H. O., TOMAN, J. E. P., AND GOODMAN, L. The lack of cerebral effects of *d*-tubocurarine. Anesthesiology, 1947, 8: 1.
41. STEAD, E. A., JR., AND WARREN, J. V. The effect of the injection of histamine into the brachial artery on the permeability of the capillaries of the forearm and hand. J. Clin. Invest., 1944, 23: 279.
42. UNNA, K. Curare-like action of erythrina alkaloids. Amer. J. Physiol., 1939, 126: 644.

43. WEST, R. The pharmacology and therapeutics of curare and its constituents. *Proc. Roy. Soc. Med.*, 1935, **28**: 565.
44. WEST, R. Intravenous curarine in the treatment of tetanus. *Lancet*, 1936, **1**: 12.
45. WEST, R. Action of curarine on respiration. *Lancet*, 1938, **1**: 432.
46. WEST, R. The action of curarine on the respiratory mechanism. *J. Physiol.*, 1938, **91**: 437.
47. WHITACRE, R. J., AND FISHER, A. J. Clinical observations on the use of curare in anesthesia. *Anesthesiology*, 1945, **6**: 124.
48. WILSON, A. T., AND WRIGHT, S. The anti-curare action of potassium and other substances. *Quart. J. Exp. Physiol.*, 1937, **26**: 127.
49. WOOLEY, L. F. Immediate circulatory and respiratory effects of curare protected metrazol and electric shock. *J. Nerv. Ment. Dis.*, 1944, **100**: 1.
50. YONKMAN, F. F., CHESS, D., MATHIESON, D., AND HANSEN, N. Pharmacodynamic studies of a new antihistamine agent, pyribenzamine HCl. *J. Pharmacol.*, 1946, **87**: 256.

PHYSIOLOGICAL STUDIES IN CONGENITAL HEART DISEASE*

III. RESULTS OBTAINED IN FIVE CASES OF EISENMENGER'S COMPLEX

R. J. BING, L. D. VANDAM, AND F. D. GRAY, JR.

From the Department of Surgery, The Johns Hopkins University and Hospital

The two previous reports in this series have dealt with physiological methods employed in the study of congenital heart disease and the results obtained from these methods in patients with tetralogy of Fallot (1, 2). This paper presents the physiological studies in 5 selected cases of congenital heart disease which had been clinically classified in the group commonly designated as Eisenmenger's complex. They were chosen out of a total of 8 similar cases since they represented most clearly the physiological and clinical aspects of this disease. The clinical findings in these cases will be discussed mainly in their relationship to the physiological data obtained.

In Eisenmenger's original publication the complex which bears his name consisted of a high ventricular septal defect, an aorta which overrode both the right and left ventricles (dextroposition of the aorta), and a dilated pulmonary artery (3). According to current concepts, the outstanding clinical features are cyanosis, which usually develops later in life, clubbing of the fingers, and in many patients the occurrence of hemoptyses (4). A loud systolic murmur is usually heard over the base of the heart to the left of the sternum. On fluoroscopy Eisenmenger's complex is characterized by a prominent pulmonary conus and marked vascular shadows with expansile pulsations in the lung fields (5).

The physiological methods used in this report have been described in detail in the first paper of this series (1). For reasons of clarity, formulae used for the determination of various volume flows by means of the Fick principle are restated and redefined at this time.

1. Pulmonary Capillary Blood Flow represents the total amount of blood flowing through the lungs.

* This study was supported by a grant from the Commonwealth Fund.

Pulmonary capillary flow ml. per min.

$$= \frac{\text{CO}_2 \text{ output ml. per min.}}{\text{CO}_2 \text{ content of blood reaching alveoli (vol. per cent)} - \text{CO}_2 \text{ content of pulmonary vein blood (vol. per cent)}} \times 100$$

Normally, pulmonary capillary flow equals pulmonary artery flow (6). In the presence of collateral circulation pulmonary capillary flow exceeds pulmonary artery flow.

2. Pulmonary Artery Flow is the blood flowing through the pulmonic valve into the pulmonary artery.

Pulmonary artery flow (ml. per min.)

$$= \frac{\text{O}_2 \text{ intake (ml. per min.)}}{\text{O}_2 \text{ content of pulmonary vein blood (vol. per cent)} - \text{O}_2 \text{ content of pulmonary artery blood (vol. per cent)}} \times 100$$

The average normal pulmonary artery flow is approximately 3000 cc./min./M² (7).

3. Oxygen content of pulmonary vein (vol. per cent) = percentage O₂ saturation of pulmonary vein \times O₂ capacity (vol. per cent). The percentage of oxygen saturation of the pulmonary vein was assumed to be 95 per cent.

4. Collateral Circulation to the Lung represents the volume flow of blood to the lung through channels other than the pulmonary artery. Collateral circulation to the lung (ml. per min.) = pulmonary capillary flow (ml. per min.) - pulmonary artery flow (ml. per min.)

5. Systemic Blood Flow is the volume of blood perfusing the systemic blood vessels.

Systemic blood flow (ml. per min.)

$$= \frac{\text{O}_2 \text{ intake (ml. per min.)}}{\text{O}_2 \text{ content of peripheral arterial blood (vol. per cent)} - \text{O}_2 \text{ content of right auricular blood (vol. per cent)}} \times 100$$

The systemic blood flow in the normal individual equals pulmonary artery flow.

6. The Intracardiac Shunt is the rate of blood flow from one ventricle to the other through a septal defect or from one ventricle into

the overriding aorta. According to its overall direction, the shunt is referred to as being from right to left or from left to right.

Intracardiac shunt right to left (ml. per min.) = volume of blood flow through the systemic circulation (ml. per min.) — volume of blood flow through the pulmonary artery (ml. per min.)

Intracardiac shunt left to right (ml. per min.) = volume of blood flow through pulmonary artery (ml. per min.) — volume of blood flow through the systemic circulation (ml. per min.)

7. The Effective Pulmonary Blood Flow is the amount of mixed venous blood which, having returned to the heart from the systemic circulation, eventually reaches the pulmonary capillaries.

Effective pulmonary blood flow (ml. per min.)

$$= \frac{\text{O}_2 \text{ intake (ml. per min.)}}{\text{O}_2 \text{ content of pulmonary vein blood (vol. per cent)} - \text{O}_2 \text{ content of right auricular blood (vol. per cent)}} \times 100$$

Normally the effective pulmonary blood flow equals pulmonary artery flow.

The assumptions made in these calculations have been discussed in detail in a previous communication. Special emphasis was placed on the difficulty in deriving the oxygen saturation of pulmonary vein blood, which was assumed to be 95 per cent. The validity of this figure has been confirmed in cases with pulmonic stenosis by analyses of blood obtained directly from the pulmonary vein (2). In patients with Eisenmenger's complex, sampling of pulmonary vein blood has been impossible. Furthermore, the question has been raised as to whether the cyanosis in Eisenmenger's complex might be the result of difficulties in the transfer of oxygen across the pulmonary alveolar membrane (8). These considerations cast some doubt on the validity of formula # 2 and 7 since it is based on the assumption that the saturation of the pulmonary vein blood is 95 per cent. If the actual saturation of pulmonary vein blood were below this value, figures obtained for pulmonary artery flow as calculated in this paper from equation 2 would be too low. The agreement between the pulmonary capillary flow and pulmonary artery flow, indicates that the calculated figures obtained for pulmonary artery flow may be accurate. Pulmonary

diffusion factors constitute a much smaller source of error in the determination of pulmonary capillary flow since the latter entails the use of carbon dioxide. The diffusion coefficient of this gas is so much greater than that of oxygen that pulmonary capillary flow should be accurate even in the presence of alveolar lesions which might develop as a sequence to vascular changes. In 2 cases, in which the elevation of pulmonary arterial pressures indicated increased resistance in the pulmonary bed, the pulmonary capillary flow equaled pulmonary artery flow. Consequently, despite increased pulmonary resistance, the values obtained with oxygen correspond to those obtained with carbon dioxide. This indicates that the use of formula 2 for the determination of pulmonary artery flow is justified in the cases reported in this paper.

Another argument against full saturation of pulmonary vein blood as implied by formula 2 has been the assumption that the intracardiac shunt was predominantly directed toward the right (8). In this case the unsaturation of peripheral arterial blood must be entirely due to pulmonary factors. This assumption was based on the belief that, in the absence of increased pulmonary resistance, the pressure in the aorta must be considerably higher than that in the pulmonary artery. Results to be described in this paper, however, show an increase in systolic and diastolic pressure in the pulmonary artery. This observation indicates increased resistance in the pulmonary vascular bed. It is probable, therefore, that mixing currents from right to left rather than unsaturation of pulmonary vein blood play the predominant role in the production of arterial unsaturation.

CASE STUDIES

Case 1. J. S. (age 10, date of study April 4, 1946). This child was apparently normal at birth. Cyanosis appeared at the age of 2 after an attack of whooping cough. Since that time moderate cyanosis had been evident on exertion. At the time of study she could walk a distance of from 3 to 4 city blocks. Her dyspnea was relieved by squatting. There was no history of hemoptysis.

On physical examination her mucous membranes were found to be slightly cyanotic. There was moderate clubbing of fingers and toes. The blood pressure was 100/70 mm. Hg in the arm. The lungs were normal to percussion and auscultation. On percussion the heart was not enlarged. On auscultation the second pulmonic sound was abnormally loud. A very soft systolic murmur could be heard along the left sternal border. There was no diastolic murmur. On

fluoroscopy the heart was of normal size. In the left anterior oblique position the pulmonary window was not well defined, and in the anteroposterior view the pulmonary conus was prominent. There were marked expansile pulsations in the lung fields. The electrocardiogram showed right axis deviation. Laboratory data revealed a hematocrit of 44 per cent, a hemoglobin of 17 gms. per 100 cc. (Sahli) and a red cell count of 4.7 millions per mm³.

Physiological studies: The standard exercise test was not performed by this patient. Table II shows that the pulmonary capillary flow was above normal limits and exceeded the pulmonary artery flow, demonstrating the presence of some collateral circulation to the lung. The significant data obtained from catheterization of the heart are illustrated in Table III and may be summarized as follows: (1) The volume flow through the pulmonary artery slightly exceeded the flow through the systemic blood vessels. (2) The oxygen content of the pulmonary artery blood exceeded that of right auricular blood by 3.4 vol. per cent. (3) The effective pulmonary blood flow was 50 per cent below the blood flow through the pulmonary arteries and the oxygen saturation in peripheral arterial blood was 83 per cent. Intracardiac pressures were not recorded.

Comment. The pulmonary artery flow exceeds the systemic flow by only 210 cc. per minute/M² (Table III). This is not considered significant evidence for a preponderant left to right shunt. Shunting currents from left to right must exist. This is indicated by the observations that the oxygen content of pulmonary artery blood exceeds that of right auricular blood by 3.4 vol. per cent and that the effective pulmonary blood flow is 50 per cent below the pulmonary artery flow. On the other hand, the presence of concomitant right to left currents is indicated by the finding that the oxygen saturation in peripheral arterial blood is reduced to 83 per cent.

Case 2. J. P. (male, aged 39. Studies begun on July 17, 1946). The patient was told that he was blue at birth. At school his activities were only slightly restricted, but with more strenuous exercise he noticed that he became more short of breath than his playmates. At 12 years of age cyanosis was noticed by the patient for the first time. He had worked for the last 17 years in occupations requiring no undue physical strain. He had had an unusual number of coughs and upper respiratory tract infections during the winter months, and in 1933 he brought up some bright red blood in one of his coughing episodes. At the age of 26 he was

told by his physician that he had congenital heart disease. Since then he has had difficulty in breathing on climbing two or three flights of stairs and had felt that the intensity of cyanosis had progressed. For the last two years he has had a dull ache in the region of the left anterior chest wall. This pain was most frequently noticed in the morning upon arising. Inhalations of oxygen and bed rest have not relieved this distress.

On physical examination there was mild cyanosis of the lips and nail beds. There was no clubbing of the fingers. The lungs were clear to percussion and auscultation. No thrill could be felt over the precordium. The area of cardiac dullness measured 11 cm. to the left in the fifth interspace and 6 cm. to the left in the second intercostal space. The heart rate was 55 beats per minute, and the rhythm was regular. The second pulmonic sound was loud and exceeded the second aortic sound in intensity. A harsh but only moderately loud systolic

TABLE I
Results Obtained from the Standard Exercise Test

NO.	DATE	NAME	SEX	AGE	VENT. LIT. MIN. M ²	CO ₂ CC. PER M ²	CO ₂ CC. PER L.V.	O ₂ CC. PER M ²	O ₂ CC. PER L.V.	R.Q.	ARTERIAL BLOOD				NO.
											O ₂ Vol. %	CO ₂ Vol. %	Cap. Vol. %	Sat. %	
2	7/17/46	J. P.	M	39	Rest 5.22	118	22.6	120	22.7	0.95	23.1	37.3	26.7	87	2
					Exer. 7.40	152	21.6	204	27.6	0.72	15.6	39.2	26.7	61	
3	11/15/46	E. S.	F	19	Rest 4.5	123	27.4	112	25.0	1.10	18.5	36.6	24.2	77	3
					Exer. 6.8	158	23.3	218	32.2	0.72	13.4	40.0	24.2	55	
4	12/11/46	V. S.	F	25	Rest 4.9	94	19.0	104	21.0	0.89	17.0	34.2	20.0	84	4
					Exer. 8.8	202	23.0	229	26.0	0.87					
5	3/12/47	B. S.	M	9	Rest 6.5	142	22.0	158	24.2	0.88	20.1	34.7	24.4	82	5
					Exer. 10.2	221	22.0	241	23.5	0.90					

murmur was heard over the fifth intercostal space half way between the point of maximum impulse and the midsternal line. A diastolic murmur was not audible. Blood pressure in the arm (by auscultation) was 125/75 mm. Hg. The hemoglobin was 19 gms. per 100 cc. of blood (Sahli). The red cell count was 7 millions per cmm. and the hematocrit was 61 per cent. The arm to tongue circulation (decho-lin) was 40 seconds (single end point). The electrocardiogram revealed left axis deviation in the standard leads.

The fluoroscopic examination showed a large pulmonary artery. There were increased vascular markings and slight pulsations in the lung fields. In the oblique views the heart did not appear enlarged.

Physiological studies: The results of the standard exercise test are summarized in Table I. It can be seen that the oxygen consumed per

liter of ventilation increased. The oxygen saturation of peripheral arterial blood drawn immediately after the exercise was lower than the resting value.

Figures obtained for the determination of pulmonary capillary blood flow are illustrated in Table II. It can be seen that the pulmonary capillary flow was at the lower limit of normal and closely approached the volume flow through the pulmonary artery. The results obtained from right heart catheterization and intubation of the pulmonary artery are shown in Table III. They may be summarized as follows: (1) The pulmonary artery flow slightly exceeded the systemic flow. (2) The blood oxygen content in the pulmonary artery was 2.7 per cent higher than that of right auricular blood. (3) The mean pressure

TABLE II
Data Obtained from Equilibration Method for Determination of Pulmonary Capillary Flow

No.	DATE	NAME	SEX	AGE	SURF. AREA M ²	CC. CO ₂ PROD.	R.Q.	MIN. VOL. L/M	CO ₂ INCOMING BLOOD			CO ₂ OUTGOING BLOOD			PULM. CAP. FLOW L/M/M ²	PULM. ARTERY FLOW L/M/M ² (CATHETER)	COLLAT. PULM. FLOW L/M/M ²	NO.
									%	mm. Hg	Vol. %	%	mm. Hg	Vol. %				
1	4/ 4/46	J. S.	F	10	1.0	106	1.3	8.3	4.53	32.0	37.5	3.96	28.0	35.1	4.25	3.65	0.60	1
2	7/18/46	J. P.	M	35	1.7	159	1.0	8.8	4.14	29.5	39.5	3.13	22.4	35.5	2.36	2.48	0	2
3	11/13/46	E. S.	F	19	1.5	163	0.9	6.9	4.70	33.7	41.8	3.8	27.6	38.4	3.11	2.20	0.91	3
4	12/ 9/46	V. S.	F	25	1.5	143	0.9	7.6	3.98	28.6	38.5	3.25	23.3	35.5	3.11	2.71	0.40	4
5	3/13/47	B. S.	M	9	0.9	99	0.7	5.2	4.40	31.8	35.3	3.1	22.4	30.5	2.23	2.28	0	5

in the pulmonary artery recorded with a saline manometer was 65 mm. Hg (Table IV). The effective pulmonary blood flow was approximately 1000 cc. less than the blood flow through the pulmonary artery and the oxygen saturation in the peripheral arterial blood was 84 per cent (Table III).

Comments. The rise in the oxygen consumed per liter of ventilation from rest to exercise demonstrates that the effective blood flow through the lung can increase sufficiently to satisfy the respiratory demands of exercise. It seems significant that the oxygen saturation of peripheral arterial blood which was drawn immediately after the performance of the exercise test is lower than the resting oxygen saturation. This is probably the result of shunting of mixed venous blood of lower oxygen saturation into the systemic circulation during and following the

TABLE III
Data Obtained from Right Heart Catheterization

MO.	DATE	NAME	SEX	AGE	SURF. AREA M ²	CC. O ₂ CONS. PROD.	CC. CO ₂	R-Q.	MIN. VOL. L/M	B.M. K.	S.V.C. O ₂ VOL. %	R.A. O ₂ VOL. %	R.V. O ₂ VOL. %	F.A. O ₂ VOL. %	F.V. O ₂ VOL. %	ARTERIAL BLOOD	CARDIAC OUTPUT	INTRA- CARD. SHUNT L/M/M ²	EFFECTIVE PULM. FLOW L/M/M ²	NO.			
1	4/ 8/46	J. S.	F	10	1.0	114	121	1.1	4.37	-32		15.8		19.2	22.2	19.0	23.1	83	3.65	3.44	.21 L-R	1.71	1
2	7/19/46	J. P.	M	39	1.7	187	164	0.9	8.4	-8		16.5	20.5	19.2	23.7	21.3	25.4	84	2.48	2.30	.18 L-R	1.53	2
3	11/15/46	E. S.	F	19	1.5	180	163	0.9	6.9	-6	13.7	14.0	15.8	17.7	23.0	18.5	24.2	77	2.20	2.60	.42 R-L	1.28	3
4	12/11/46	V. S.	F	25	1.5	205	200	1.0	9.3	+2	11.6	11.6	14.7	14.1	19.0	16.8	20.0	83	2.71	2.56	0.15 L-R	1.80	4
5	3/12/47	B. S.	M	9	0.9	111	113	1.0	6.0	-31	14.3	14.3	15.3	16.1	21.4	18.7	22.5	83	2.28	2.72	0.44 R-L	1.70	5

TABLE IV
Intraventricular and Peripheral Blood Pressures. Resistances in the Pulmonary and Peripheral Circulation

NO.	DATE	NAME	SEX	AGE	FEMORAL ARTERY MM. Hg			SYSTEMIC FLOW LITERS/MIN.	PERIPHERAL RESISTANCE DYNES-CM ² PER SECOND	RIGHT VENTRICLE MM. Hg		PULMONARY ARTERY MM. Hg		PULMONARY ARTERY FLOW LITERS/MIN.	PULMONARY RESISTANCE DYNES-CM ² PER SECOND	NO.
					Syst.	Diast.	Mean			Syst.	Diast.	Syst.	Diast.			
2	7/19/46	J. P.	M	39	120	75	90	3.9	1850					4.2	1260	2
3	11/15/46	E. S.	F	19	134	82	102	4.0	2020	97	36	122	86	3.4	2300	3
4	12/11/46	V. S.	F	25	122	79	95	3.9	1920	112	0	112	64	4.2	1545	4
5	3/12/47	B. S.	M	9			100	2.5	3180	137	12		100	2.1	3800	5

* Mean pressure recorded with a saline manometer. All other pressures in this table recorded with the Hamilton Manometer.

exercise. Results obtained from catheterization of the right auricle, the right ventricle, and the pulmonary artery demonstrate that the pulmonary artery blood flow exceeds systemic blood flow by 180 cc. per min./M². This figure is too low to be considered an indication of a preponderant left to right shunt. On the other hand, the following observations indicate extensive interventricular admixture of blood: The oxygen content of pulmonary artery blood exceeds that of right auricular blood by 2.7 volumes per cent, and the effective pulmonary artery flow is 1000 cc. less than the volume flow through the pulmonary artery. These findings indicate large left to right currents. The reduction of the peripheral arterial oxygen saturation to 83 per cent, however, demonstrates that some of the interventricular currents are flowing from the right ventricle into the overriding aorta. The negligible value derived for the intracardiac shunt and the evidence for extensive interventricular admixture of blood make it probable that the volumes of the mixing currents from right to left and from left to right are about equal.

Case 3. E. S. (age 19 years, date of study November 13, 1946). The patient was supposedly normal at birth. When she was 4 years old her parents consulted a physician because she had begun to exhibit marked breathlessness with moderate exercise. At that time she was found to be slightly cyanotic at rest. Her condition had remained the same until she was 15 years old when shortness of breath became apparent during the slightest exertion. The shortness of breath could be relieved by squatting. Since then she had had spells of dizziness and palpitation which lasted several minutes at a time. There had been no episodes of hemoptysis.

On physical examination her lips were slightly cyanotic and there was minimal clubbing of the fingers and toes. There were no abnormal physical findings in the lungs. The heart was not enlarged on percussion. There was a slight systolic thrill felt over the base of the heart. On auscultation a very low pitched systolic murmur was heard. This murmur increased in intensity during mild exercise. No diastolic murmur was heard.

The red cell count was 6 millions per cmm. The hemoglobin was 17.5 gm. (Sahli). The volume of packed red cells was 57.3 per cent. The electrocardiogram showed right axis deviation in the standard leads and right ventricular hypertrophy in the chest leads.

On fluoroscopy the heart appeared to be of normal size. The pulmonary conus was full and expansile pulsations in the lung fields could be seen.

Physiological studies: Table II shows that the pulmonary capillary flow was within normal limits. However, it exceeded pulmonary

artery flow by 900 cc. The results of the standard exercise test are illustrated in Table I. It can be seen that the ratio of carbon dioxide produced per liter of ventilation fell from rest to exercise; the ratio of oxygen consumed per liter of ventilation, on the other hand, rose. The arterial oxygen saturation determined immediately following the exercise was considerably lower than the resting value. The significant

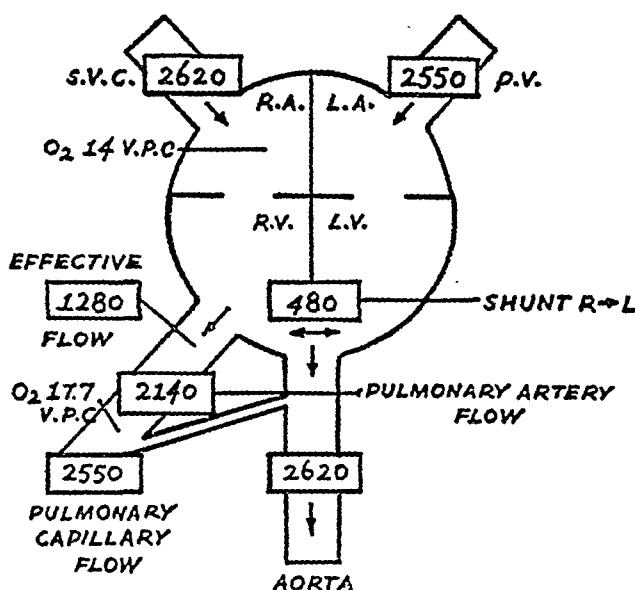


FIG. 1. ILLUSTRATES THE FINDINGS IN PATIENT #3 (E. S.) AGE 19.

It may be seen that the systemic flow exceeds pulmonary artery flow, giving the intracardiac shunt an overall direction of from right to left. The pulmonary artery, however, receives oxygenated blood from the left side of the heart, since the oxygen content of pulmonary artery blood exceeds the oxygen content of right auricular blood.

results obtained by catheterization of the heart may be summarized as follows (Fig. 1 and Table III): (1) The systemic flow exceeded pulmonary artery flow by 400 cc. (2) The effective pulmonary blood flow was 60 per cent of the pulmonary artery flow. (3) The oxygen concentration of the pulmonary arterial blood closely approached that of femoral artery blood, while exceeding that of right ventricular and auricular blood by 1.9 and 3.7 vol. per cent respectively (the right

ventricular sample was collected near the tricuspid valve). (4) The oxygen saturation in peripheral arterial blood was 77 per cent. (5) The pressures in the right ventricle were 97/36 mm. Hg, those in the pulmonary artery 122/86 mm. Hg. Pulmonary artery and right ventricular pressures were not recorded simultaneously. This probably explains the difference in the height of the respective systolic pressures (Table IV).

Comments. The value obtained for pulmonary capillary flow is similar to that recorded in normal individuals (6). They exceed considerably, however, pulmonary artery flow, indicating the presence of some collateral circulation to the lung. The results obtained with the standard exercise test conform to those obtained in the previous cases. Since pulmonic stenosis is probably absent, the effective pulmonary blood flow can increase during exercise in proportion to the minute volume of respiration. This results in a rise in the ratio oxygen consumed per liter of ventilation. The findings obtained with the catheterization of the heart are illustrated in Table III and Figure 1. In contrast to the previous case, the systemic blood flow is slightly greater than that through the pulmonary artery, with the result that the overall direction of the intracardiac shunt is directed from right to left. On the other hand, the large difference in the oxygen content between blood from the right auricle and the right ventricle and the pulmonary artery respectively indicates that the pulmonary artery receives oxygenated blood from the left side of the heart. This conclusion is also supported by the fact that the effective pulmonary blood flow is 50 per cent that of the pulmonary artery flow. The aorta, however, receives a large amount of mixed venous blood. This is indicated by the reduced oxygen saturation of peripheral arterial blood.

The pressures recorded from the right ventricle and the pulmonary artery show an elevation of the systolic and diastolic pressures in the pulmonary artery and the right ventricle above their normal values. It is possible that the abnormally high diastolic pressure recorded in the right ventricle of this patient is the result of an insufficiency of the pulmonic valve, although clinical evidence for this is lacking.

Case 4. V. S. (age 25, studies begun December 9, 1946). The patient is said to have been blue at birth. She related that she had been short of breath as

long as she could remember. In 1943 she had had a normal full term pregnancy and since then had had repeated hemoptyses, which at first amounted to little more than blood streaked sputum; during the last year the hemoptyses had become more extensive, occurring characteristically during the ten to twelve days before the onset of menstruation. She had had her most serious hemoptysis a year before admission when she is said to have coughed up about a quart of fresh blood. Immediately following this she was admitted to a hospital where she remained for several days. Since then hemoptyses had not occurred. At the time of admission for study she had no complaints although her exercise tolerance was impaired.

On physical examination a slight degree of cyanosis of the lips was present. There was marked clubbing of fingers and toes. The lungs were normal on percussion and auscultation. The blood pressures in the arm (auscultation) were 120/75 mm. Hg. The heart was not enlarged to percussion and there was no thrill. A loud systolic murmur could be heard over the whole left anterior chest wall, with its maximum intensity at the left sternal border. No diastolic murmur was audible.

On fluoroscopic examination the right auricle and ventricle seemed to be enlarged. This was particularly apparent in the left anterior oblique position. There were flatness in the region of the pulmonary conus and increased vascular markings in both lung fields which showed definite expansile pulsations. The hemoglobin was 15.0 gms. per 100 cc. (Sahli). The red blood cell count was 5.4 millions per cmm. and the hematocrit was 49 per cent. The electrocardiogram revealed right axis deviation in the standard leads.

Physiological studies: The results of the standard exercise test are illustrated in Table I. Both the ratios carbon dioxide and oxygen produced and consumed per liter of ventilation increased during the exercise test. The peripheral oxygen saturation could not be determined, but it was observed that the cyanosis increased immediately following the exercise. Table II demonstrates that the pulmonary capillary flow was within normal limits and slightly exceeded the pulmonary artery flow. The results of catheterization of the heart are illustrated in Table III and Fig. 2. It can be seen that (1) the volume of blood flowing through the pulmonary artery was of the same order as that perfusing the systemic capillaries; (2) the effective pulmonary blood flow was considerably lower than the pulmonary artery flow; (3) the oxygen content of pulmonary artery blood exceeded that of right auricular blood by 2.5 vol. per cent; (4) the systolic pressure in the right ventricle was 112 mm. mercury (Table IV), which represents an elevation of approximately 80 mm. of Hg above normal ventricular

pressures recorded by Cournand (7). The blood pressures in the pulmonary artery were also increased (Table IV).

Comments. The rise in the ratio oxygen consumed and carbon dioxide produced per liter of ventilation obtained during the standard exercise test indicates that the effective pulmonary blood flow increases

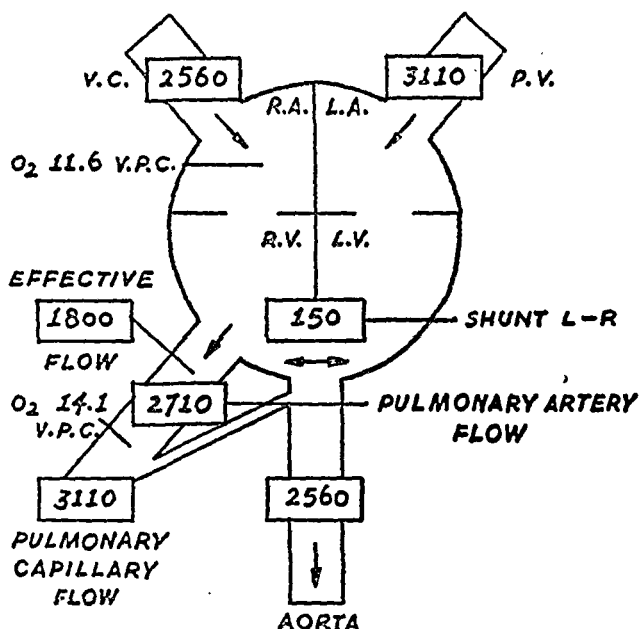


FIG. 2. SHOWS THE FINDINGS IN PATIENT #4 (V. S.) AGE 25

There is a slight preponderance of the overall intracardiac shunt from left to right. The observation that the effective pulmonary blood flow is less than the pulmonary artery flow and the finding of a large difference between the oxygen contents of pulmonary artery and right auricular blood indicate left to right mixing currents.

sufficiently to take care of the respiratory demands of exercise. The absence of significant collateral circulation to the lung is demonstrated by the fact that the difference between pulmonary capillary flow and pulmonary artery flow is small (Table II and Fig. 2). Similarly, as in the previous case, there is no preponderant direction of the inter-ventricular mixing currents. This is indicated by the observations

that pulmonary artery flow almost equals systemic flow (Table III and Fig. 2). It is probable, however, that interventricular admixture of blood takes place. This assumption is supported by the following facts: The oxygen content of the pulmonary artery blood exceeds that of right auricular blood by 2.5 vol. per cent; the effective pulmonary blood flow is 1000 cc. less than the pulmonary artery flow, and the

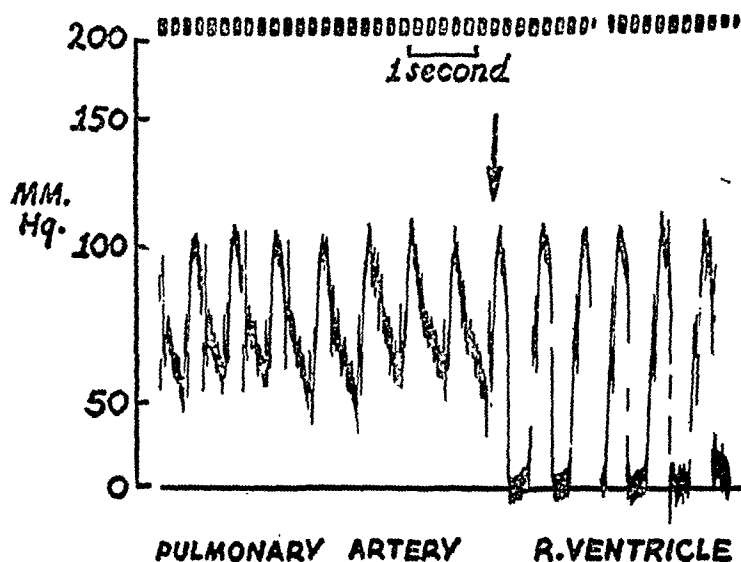


FIG. 3. ILLUSTRATES CONTINUOUS OPTICAL PRESSURE RECORDINGS OBTAINED FROM THE PULMONARY ARTERY AND THE RIGHT VENTRICLE OF PATIENT #4 (V. S.) AGE 25.

The record demonstrates high systolic and diastolic pressure in the pulmonary artery. Withdrawal of the catheter tip through the pulmonic valve into the right ventricle (arrow in figure) results in a sharp fall of the diastolic pressure to zero. The systolic pressure remains constant.

resting arterial oxygen saturation is below normal (Table III and Fig. 2). Of special interest are the blood pressures recorded from the pulmonary artery. As seen in Figure 3 and Table IV, the systolic and diastolic pressures in that vessel are greatly increased above the normal values of 25/8 mm. Hg which have been recorded from the pulmonary artery of normal individuals (7). The systolic pressure in the right ventricle is also greatly increased. The significance of these pressure readings and their diagnostic importance will be discussed below.

Case 5. B. S. (male, aged 9, date of study March 12, 1947). This patient appeared to be entirely normal at birth. At the age of four months his parents had noticed that his heart beats were unduly rapid. In the second year of his life blueness of the lips and fingernails had become apparent and had persisted ever since with increase in intensity on exertion. The child's activities had always been limited by shortness of breath. In the two years prior to examination there had been a gradual decrease in exercise tolerance so that at the time of entry the child could hardly walk a city block or mount a flight of stairs. There had always been a marked tendency toward contraction of respiratory infections. No history of hemoptysis could be elicited.

Physical examination: The child appeared underweight and the posture was poor. Mild cyanosis and clubbing of the digits were evident. The lungs were clear to percussion and auscultation. The area of cardiac dullness was not increased and a shock was felt over the precordium. The second heart sound was particularly loud in the fourth left interspace. A short harsh systolic murmur heard maximally over the third and fourth left interspaces could also be heard bilaterally in the interscapular regions. A diastolic murmur was not audible. The blood pressure in the arms was 110/90 mm. Hg.

Laboratory data: The red blood cell count was 5.75 millions per cmm, the hemoglobin 15.9 gms. (Sahli), the hematocrit 48 per cent and the arm to tongue circulation time (decholin) was 10 seconds.

Under the fluoroscope the heart seemed enlarged in both the anteroposterior and transverse diameters with the left ventricle more prominent than normal. Active pulsations were seen in the region of the pulmonary conus. The hilar markings were increased but active pulsations in the lung fields were not present.

Physiological studies: On performance of the standard exercise test both oxygen consumed and carbon dioxide produced per liter of ventilation remained approximately constant (Table I). The arterial oxygen saturation was not obtained immediately following the exercise, but it was felt that the patient showed a marked increase in cyanosis.

The pulmonary capillary flow, shown in Table II, was reduced to about 75 per cent of the average normal index. However, since it was equal to the pulmonary artery flow, collateral circulation was not present. Other data obtained from right heart catheterization are summarized in Table III which contains the following observations: (1) The flow through the systemic circulation exceeded that through the pulmonary artery by about 20 per cent, resulting in a right to left intracardiac shunt of 440 cc./M²; (2) the oxygen content of the pulmonary artery blood was within 2 volumes per cent of that in the right auricle; (3) the effective pulmonary flow was only 75 per cent of the

flow in the pulmonary artery, and the peripheral arterial blood oxygen saturation was reduced to 83.4 per cent.

Pulmonary artery and peripheral arterial pressures, shown in Table IV, were dampened, hence only mean values could be derived from the tracings. In each case a mean pressure of 100 mm. of Hg was found. In the right ventricle a systolic pressure of 137 mm. of Hg and a diastolic pressure of 12 mm. of Hg were recorded.

Comments. The failure of the oxygen consumed per liter of ventilation to rise during exercise indicates that the effective pulmonary flow fails to increase normally during exercise (Table I). This observation is consistent with the finding that the pulmonary artery flow is reduced below the normal index (Table III).

Although the oxygen content of pulmonary artery blood is not greatly different from that in the right auricle, left to right admixture of ventricular blood must take place as the effective pulmonary flow is less than the pulmonary artery flow (Table III). The existence of right to left admixture is demonstrated by the lowered peripheral arterial oxygen saturation (Table III). There is a sufficient overall right to left shunt of 440 cc. (Table III)

The findings in this case resemble those in patient 3 (E. S.). As in case 3 the pulmonary artery flow is decreased and the overall direction of the intracardiac shunt is directed from right to left. In these respects the dynamics of both cases resemble those reported previously in tetralogy of Fallot (2). Pulmonic stenosis is absent, however, since the mean pressure in the pulmonary artery is elevated. In these two patients (B. S., #5, and E. S. #0) the calculated pulmonary resistance is considerably elevated (Table IV) and exceeds the peripheral vascular resistance. Consequently, in the absence of pulmonic stenosis, the predominant right to left intracardiac shunt must be the sequence of increased resistance in the smaller vessels of the pulmonary vascular tree.

DISCUSSION

The clinical histories of the 5 patients who are the subjects of this report reveal that dyspnea on ordinary exertion developed during childhood. Two of them had repeated episodes of hemoptyses. In case #4, V. S., the hemoptysis was so severe on one occasion that it necessitated hospitalization. On inspection, moderate clubbing of the

fingers and toes and mild cyanosis were found in all cases. On physical examination of the heart a systolic murmur was audible in every instance. No diastolic murmur could be heard. The lungs were clinically normal. Laboratory data revealed that the hemoglobin content varied from 15 to 19 gm. per 100 cc. of blood, the red cell count from 5 to 7 millions per cmm., and the hematocrit from 48 to 68 per cent. The electrocardiograms showed right axis deviation in 3 cases. One patient (J. P., #2) had left axis deviation. On fluoroscopic examination, expansile pulsations in the lung field were seen in 4 of the 5 cases. Fullness of the pulmonary conus was present in 4 patients. In one case (V. S., #4) the pulmonary conus was not prominent.

An analysis of the physiological data demonstrates that the performance of the standard exercise test was accompanied in 4 out of 5 cases by a rise in the ratio of oxygen consumed per liter of ventilation (Table I). In one patient (B. S., #5) it remained constant. This finding contrasts with that obtained in most patients with tetralogy of Fallot, in whom this ratio declines during exercise (2). The rise in this ratio furnishes evidence that the effective pulmonary blood flow can increase during exercise. In tetralogy of Fallot, pulmonic stenosis limits the effective pulmonary blood flow during exercise and the ratio oxygen consumed per liter of ventilation declines (2). The oxygen saturation in the peripheral arterial blood fell in 3 cases, as it did in tetralogy of Fallot (2). In the other 2 cases, in whom the arterial oxygen saturation was not obtained, cyanosis was visibly increased after exercise. It is probable that this is the result of increased shunting of venous blood into the overriding aorta, shunting of venous blood with lower oxygen saturation, or a combination of both. The physiological data obtained with the standard exercise test, therefore, reveal the importance of this test in differentiating cases with adequate pulmonary flow from those in whom pulmonary blood flow is decreased. Consequently, it has been of value in the preoperative selection of patients for operation.

In 2 patients (E. S., #3, and V. S., #4) the pulmonary capillary blood flow was within normal limits (6). In 2 others (J. P., #2, and B. S., #5) the pulmonary capillary flow was slightly decreased, while in J. S. (#1) it was above normal. Table II indicates that in 2

patients (J. P., #2, and B. S., #5) values for pulmonary capillary flow approached those obtained for pulmonary artery flow, indicating the absence of significant collateral circulation to the lung. In 3 individuals (J. S., #1, E. S., #3, and V. S., #4) some increase in the collateral circulation to the lung was present, since pulmonary capillary flow exceeded that through the pulmonary artery. It is impossible at the present moment to ascertain why some individuals of this series have collateral circulation while others have not.

A comparison of the values obtained for pulmonary artery flow and systemic blood flow shows that the pulmonary artery flow slightly exceeded the systemic blood flow in 3 cases (J. S., #1, J. P., #2, and V. S., #4) (Table III and Fig. 2). These findings indicate that in these patients there is a slight preponderance of the intracardiac shunt toward the right. In E. S. (#3) and B. S. (#5), however, the overall direction of the intracardiac shunt was from right to left since the systemic flow was larger than the pulmonary artery flow (Table III and Fig. 1). Irrespective of the overall direction of the intracardiac shunt, interventricular mixing currents existed in all patients. Left to right admixture is indicated by the relatively high values for the oxygen contents of pulmonary artery blood and by the low values obtained for effective pulmonary blood flow. On the other hand, the decrease in the peripheral oxygen saturation demonstrates the presence of right to left currents.

These observations are of considerable interest since they permit certain assumptions to be made concerning the nature of pulmonary hemodynamics. If the total cross-sectional area of the pulmonary arteriolar bed were normal in the absence of pulmonic stenosis, the intracardiac shunt would be predominantly directed toward the right. The preceding discussion indicated, however, that in 3 patients the overall volume of blood shunted from left to right was insignificant. In 2 individuals there was a significant right to left shunt. In all instances pulmonic stenosis was absent since both systolic and diastolic pressures in the pulmonary artery were elevated. These observations indicate, therefore, an increase in the vascular resistance of the pulmonary bed.

This conclusion is further substantiated by the pressures recorded from the pulmonary artery (Table IV). It can be seen that in all

of them the mean pressure in this vessel is elevated above normal values. In E. S. (#3) and V. S. (#4), in whom systolic and diastolic pressures were recorded, both pressures are increased (Fig. 3). It is probable that in the presence of normal blood flow the elevation of the diastolic pressures above normal values of approximately 8 mm. Hg (7) represents the result of increased resistance in the pulmonary bed. This assumption is supported by the findings represented in Table IV. It is seen here that the calculated resistance in the pulmonary vascular tree is increased considerably over the normal of 300 dynes/cm⁵/sec.¹ In 2 patients (J. P., #2, and V. S., #4) the pulmonary vascular resistance is slightly below the peripheral resistance. In 2 cases (E. S., #3, and B. S., #5) the pulmonary resistance exceeds the peripheral resistance.

The increase in the resistance in the pulmonary bed is also illustrated by changes which occur in the energy expended by the right ventricle of these patients. It is realized that in addition to the assumptions usually made in the calculations of the work of the normal heart, further assumptions have to be made in the cases under discussion. This will greatly detract from the accuracy of the results obtained. Nevertheless it is felt that the calculation of the work of the heart might further contribute to an understanding of the principal hemodynamic changes in this complex disease.

It is customary in the calculation of the work of the heart to distinguish between velocity and pressure energy (10). Since the velocity energy is usually small, and since its calculation is based on figures of doubtful accuracy, it is usually neglected in the estimation of the work of the heart. In the cases discussed in this paper the relative changes between velocity and pressure forms of energy are of importance. Therefore it has been necessary to calculate both forms of energy.

In these calculations the components for pressure and velocity energy are computed with reference to the aorta and the pulmonary artery only. No attempt is made to include the energy contents of the blood passing through the interventricular septal defect. The

¹ The figure of 300 dynes/cm⁵/sec. was derived from an application of Aperia's formula (9), using accepted normal values for cardiac output and mean pulmonary arterial pressure.

facts which would permit these calculations are too difficult to ascertain. Furthermore, the volume of the overall intracardiac shunt is too small to make the energy contents of the blood shunted through the defect significant.²

The chief assumptions made in calculating the energy relationships were the crosssectional areas of the aorta and the pulmonary artery. The figures for crosssection areas used were compiled from normal autopsies (11). It is conceivable that in the patients who form the subject of the present discussion the pulmonary hypertension led to an increase in the crosssectional area of the pulmonary artery over the normal. Another difficulty in evaluating the data obtained arises from the fact that the energy expenditure of the heart varies directly with the cardiac output and the mean blood pressure and indirectly with the crosssectional area of the large vessels. It is known that all these factors are determined by individual characteristics such as age and sex. Consequently, it is difficult to interpret the values obtained

¹ The formulae used in the calculation of the work of the ventricle are derived from Starling (10).

$$(1) \quad \text{Pressure energy (Gram-cms.)} = \text{M.P.} \times \text{S.D.} \times \text{D. Hg.}$$

where M.P. = Mean Blood Pressure in the pulmonary artery or aorta (mm. Hg)

S.D. = Systolic Discharge (cc./min.)

D. Hg = Density of Mercury

$$(2) \quad \text{Velocity energy (Gram-cms.)} = \frac{V_A \times \text{S.D.}}{2g}$$

where V_A = Velocity of blood in pulmonary artery or aorta (Cms./sec.)

S.D. = Systolic Discharge (cc./min.)

g = gravity constant

V_A The flow velocity in the pulmonary artery or aorta was calculated according to the formula:

$$(3) \quad V_A \text{ (Cms./sec.)} = \frac{\text{SD}}{C_A \times \text{ET}}$$

where S.D. = Systolic Discharge (cc./min.)

C_A = Cross Section area of pulmonary artery or aorta (Cms²)

ET = Systolic Ejection period (sec.)

The systolic ejection period was calculated according to the formula:

$$(4) \quad \text{Systolic ejection period (sec.)} = \frac{60/\text{Pulse rate}}{8/3}$$

$$(5) \quad \text{Systolic discharge (cc./min.)} = \frac{\text{Minute volume (cc min.)}}{\text{Pulse rate (beats per minute)}}$$

for velocity or pressure energy by relating them to normals. Some conclusions, however, may be drawn by relating the velocity energy of each ventricle to total work and by comparing the work of each chamber with that of the whole heart. These relationships can then be compared with those existing in the normal.

It may be seen in Table V that in the right ventricle of the 2 patients the ratio $\frac{\text{velocity energy}}{\text{total work}}$ is one tenth of the normal. Normally the

ratio $\frac{\text{velocity energy}}{\text{total work}}$ is 5 times as great in the right ventricle as in the

left (Table V). In the 2 patients, on the other hand, this ratio is reversed, being greater in the left than in the right ventricle. This is to be expected since normally the right ventricle is not working against high pulmonary resistance. Similar calculations made for the ratio $\frac{\text{velocity energy}}{\text{total work}}$ of the left ventricle approach normal values (Table V).

This demonstrates that the energy expenditure of the right ventricle in overcoming pulmonary resistance is proportionally as large as that expended by the left ventricle in the overcoming of peripheral resistance.

The last column in Table V illustrates the relationship of the total work of the right ventricle to that of the whole heart. It can be seen that normally the right ventricular component is small compared to that of the whole heart. In the 2 cases illustrated in Table V, however, the work done by the right ventricle comprises almost one third to one half of that of the total work of the heart. It is evident that the increase in the ratio right ventricular work to that of the whole heart is the result of increased resistance in the pulmonary bed. This forces the right ventricle to raise the pressure energy expenditure in order to maintain adequate blood flow through the lung. It is difficult to ascertain the anatomical lesion responsible for an increase in pulmonary resistance since reports of the microscopic pathology of lung tissue in congenital heart disease with increased pulmonary arterial pressure have not been published. Burnett and White (12), however, report endarteritic changes in the pulmonary arterioles in 2 cases of large interauricular septal defect. It is conceivable that similar lesions exist

TABLE V
The Work of the Heart in Two Cases of Eisenmenger's Complex

NO.	DATE	NAME	SEX	AGE	RIGHT HEART										LEFT HEART										NO.	
					Systol. Discharge cc.	Cross sec. Area Cm ²	Systol. Eject. Time Seconds	Velocity Cm./Sec.	Velocity Energy Cm.-cms.	Pressure Energy Cm.-cms.	Mean Pressure mm.Hg	Total Work Cm.-cms.	Vel. energy $\times 100$	Systol. Discharge cc.	Cross Sec. area Cm. ²	Systol. Eject. Time Seconds	Velocity Cm./Sec.	Velocity Energy Cm.-cms.	Pressure Energy Cm.-cms.	Mean Pressure mm.Hg	Total Work Cm.-cms.	Vel. energy $\times 100$	Total work $\times 100$	TOTAL WORK OF WHOLE HEART		WORK OF RIGHT HEART $\times 100$
Normal					66.5	5.14	.3	43	1.46	1360	15	1361.5	.11		66.5	3.9	.3	57.0	1.91	9050	100	9051.9	.0214	10113.0	13	Normal
3	11/15/46	E. S.	F	19	36.7	5.14	.25	28.4	.53	4850	98	4850.5	.011		44.5	3.9	.25	46.0	1.04	6200	102	6231	.0162	11051.5	43.5	3
4	12/11/46	V. S.	F	15	46.0	5.14	.25	35.7	.84	5000	80	5000.8	.017		50.5	3.9	.25	52.0	1.35	6500	95	6501	.02	11501.8	43.5	4

* Values for the work of the normal heart were derived from the following figures:

minute volume = 5000 cc./min.; pulse rate = 75/min.; cross section area of pulmonary artery = 5.14 cm^2 ; cross section of aorta = 3.9 cm^2 . Mean pressure in pulmonary artery = 15 mm. Hg. Mean pressure in aorta = 100 mm. Hg.

in the cases reported in this paper. Unpublished observations from the Department of Pathology of the Johns Hopkins Hospital on several cases of dilatation of the pulmonary artery with septal defects in infants have demonstrated generalized narrowing of the lumina of pulmonary arterioles due to thickening of the media and intima. Of special significance were the findings that the pulmonary alveolar walls were normal (13).

The results obtained from the study of the patients discussed in this series make it apparent that these cases belong both clinically and physiologically to a common group, which has been designated "Eisenmenger's complex." Gross pathological observations make it clear that this complex is distinguished from the tetralogy of Fallot by a normal or dilated pulmonary artery (4). Quantitative physiological observations of this disorder have not been published to our knowledge. In his original paper Eisenmenger assumed that the intracardiac shunt was predominantly directed from left to right. The results described in this paper indicate that Eisenmenger's complex is characterized by pulmonary hypertension, by normal or reduced pulmonary artery flow, and by a reduction in the effective pulmonary blood flow. The resistance in the pulmonary vascular tree is increased and the intracardiac shunt is directed both from right to left and from left to right.

SUMMARY

Five cases of Eisenmenger's complex have been studied.

The performance of the standard exercise test was accompanied in 4 out of 5 cases by a rise in the ratio of oxygen consumed per liter of ventilation. The ratio remained constant in one patient. These findings are in contrast to those obtained in patients with tetralogy of Fallot, in whom the ratio oxygen consumed per liter of ventilation usually declines.

In 3 patients there was a slight preponderance of the intracardiac shunt from left to right. In 2 patients the overall direction of the intracardiac shunt was toward the left. Irrespective of the overall direction of the intracardiac shunt, interventricular admixture of blood existed in all cases.

Increased resistance in the pulmonary bed was indicated by the following findings:

a. A left to right intracardiac shunt was either small or absent.
 b. Both systolic and diastolic pressures in the pulmonary artery were elevated.

c. The ratio $\frac{\text{velocity energy}}{\text{total work}}$ calculated for the right ventricle was one tenth of the normal, and the work of the right ventricle comprised one third to one half of the total work of the heart.

The relationship of these findings to clinical observations was discussed.

REFERENCES

1. BING, R. J., VANDAM, L. D., AND GRAY, F. D., JR.: Physiological Studies in Congenital Heart Disease. I. Procedures. Bull. Johns Hopkins Hosp. 80: 107, 1947.
2. BING, R. J., VANDAM, L. D., AND GRAY, F. D., JR.: Physiological Studies in Congenital Heart Disease. II. Results of Preoperative Studies in Patients with Tetralogy of Fallot. Ibid., 80: 121, 1947.
3. EISENMENGER, V.: Die angeborenen Defekte der Kammerscheidewand des Herzens. Ztschr. f. Klin. Med. Vol. 32 (Supplement), 1897.
4. ABBOTT, M. E.: Congenital Cardiac Disease. In Vol. IV of Osler's Modern Medicine. Lea and Febiger, Phila., 3d ed. 1927.
5. TAUSSIG, H. B.: Clinical Analyses of Congenital Malformations of the Heart. The Commonwealth Fund (In Press).
6. GRAY, F. D., JR., BING, R. J., AND VANDAM, L. D.: A Comparison of Measurements of Cardiac Output Using the Direct Fick Principle and a Method Involving Carbon Dioxide Equilibration. To be published.
7. Cournand, A.: Recent Observations on the Dynamics of the Pulmonary Circulation. Bull. New York Acad. Med. Vol. 23 (2d Series) 27, 1947.
8. BURWELL, C. S.: Studies of the Circulation in Congenital Affections of the Heart and their Application to some of the Problems of Heart Disease. Trans. and Stud. Col. Physicians of Phila. 10: 82, 1942-43.
9. Aperia, A.: Hemodynamic Studies. Skand. Arch. f. Physiol. Suppl. 16 (to Vol. 83), 1940.
10. Starling's Principles of Human Physiology. Ed. by C. L. Evans. Lea and Febiger, Phila. 7th ed. 1936.
11. SAPHIR, OTTO: Autopsy Diagnosis and Technique, Hoeber, New York, 2nd ed., 1946.
12. BURNETT, J. B., AND WHITE, P. D. Large Interatrial Septal Defect with Particular Reference to Diagnosis and Longevity. Am. J. Med. Sci. 209: 355, 1945.
13. DANDY, W. E., JR. To be published.

THE IMPACT OF MODERN PSYCHIATRY ON MEDICAL EDUCATION, MEDICAL PRACTICE, AND HOSPITAL ORGANIZATION

LAWRENCE S. KUBIE, M.D.

The class which graduated from the Johns Hopkins Medical School in 1921 has been unique with respect to the number of graduates who have become psychiatrists. Five of us interned in the Phipps; and since then several others have joined our ranks. This must have something to do with the fact that I was selected to represent the class at this reunion. It is an honor and an opportunity which I appreciate deeply; but there are many others in the class who in the intervening quarter-century have made more significant contributions to medical science than I have.

I am embarrassed at the somewhat grandiose scope of the title of this paper. On such a topic there is either very little to say, and that quite obvious, or else so much to say that one could talk for hours. I want to talk to you slowly for emphasis, because I feel deeply about these matters; and on the other hand I want to talk as rapidly as I can in order to cover as much ground as possible. I remind myself of a patient who talked so rapidly that I could barely understand him. One day he suddenly caught his breath and said, "The reason I talk so fast is so that I can get my money's worth." To be here today, with the privilege of presenting to you certain views which I have developed over the years, is more than my money's worth. And since it would take a hundred minutes instead of thirty to cover this subject, I will begin by wasting a few moments by referring briefly to two basic issues which I cannot discuss fully.

There are two problems in the structure of medicine, the solution of which is a necessary prelude to a happy marriage between psychiatry and organic medicine: the economic organization of medicine, and the emotional immaturity of our educational system. With more time it would be easy to demonstrate that economic insecurity stands between psychiatry and organic medicine, turning initial eagerness into rivalry, fear, and hostility. Similarly psychological immaturity converts initial interest into outrage and incomprehension. For

these basic problems the only cure is a sounder social and medical economy, and a more mature educational system from the nursery years on up. An adequate discussion of these topics is beyond the scope of this brief paper.

Nor will I give you the speech which is expected of a psychiatrist when he addresses a group of internists and surgeons. I will give you no defense of psychiatry. I will present no illustrative case histories. I will assume that you have heard all of this many times; and that in theory we are in agreement about the deepening part that psychiatry is destined to play in modern medicine. Instead, on the strength of that comfortable assumption, I will go directly to my theme.

In the 25 years which we celebrate today psychiatry has changed far more than is generally realized,—changed even more than these familiar halls. For a primary preoccupation with the psychoses it has substituted a primary preoccupation with the neuroses. True there are 600,000 overcrowded beds for psychotic patients in the country; and as many more patients on parole or in remissions or discharged as socially adjusted. This however is nothing compared to the numbers of human beings with frank symptomatic neuroses, variously estimated in this country as between 6 and 12 millions: estimates which are conservative when we take into consideration the masked personality neuroses as well, a group which it will be my argument that medicine can no longer ignore.

This shift in the field of work of the psychiatrist creates a large and difficult challenge for all of medicine. To understand its full implications we must stop for a moment to consider how it has come about. As always in medicine changes result not from new words, but from new techniques and their courageous and dogged if blundering application. The technique that has wrought this change is psychoanalysis: because it was our first method for a systematic exploration of conscious and unconscious levels of the personality. This is not to say that psychoanalysis is a perfect instrument, or that it is the ultimate answer. Far from it. In his own summary of psychoanalysis in the 1926 edition of the *Encyclopedia Britannica*, Freud himself said explicitly that in the long and retrospective view of science, psychoanalysis will be seen to have been important not as a technique of treatment but as a first approach to a scientific understanding of

human nature. This understanding has been won through bitter and often heart-breaking struggles to analyze the neurotic process, both in those states of decompensation which we call neuroses, and in the masked neurotic process which influences the daily lives of all of us. There will be better and briefer methods of treatment; but it is worth a word of warning that we do not possess them yet, that although we are working on them and moving towards them, premature claims should be heard with careful scepticism. . . .

In the meantime the study of human nature, like the study of physiology, proceeds from the investigation of pathological deviations (i.e. neuroses) to the study of the normal. Here again, psychiatry is recapitulating the history of medicine in general. Twenty-five years ago in these United States only about 50 men were attempting to deal with the neuroses, either in private practice or in community agencies. Of these 50 about 20 called themselves analysts, only a few with any real right to the name. Today there are nearly 400 well-trained analysts in the country. In New York City, 125 physicians are members of the New York Psychoanalytic Institute which is training about 120 physician-students: and nearly 150 applications are on file for next year, largely from veteran medical officers. This is an indication of the change which is in progress within psychiatry itself. When I think of the past I am amazed at the change in our medical and cultural outlook which has been started by these few students of human nature and its subtle pathology. I am tempted to paraphrase Churchill and say, "Rarely in the history of medical science has so much been owed to so few."

At the same time I might add that I am also amazed by the persistent power of the neurotic forces in human nature which make it so difficult for us to learn either from our own experiences or from those of others. Again and again medical schools which made obvious and predictable blunders in their choices of psychiatric leaders a quarter of a century ago, today are repeating these errors by placing the choice in the hands of those who are devoid of any understanding of the needs of modern psychiatry, and who are actively hostile to psychiatry, or into the hands of those who still think of psychiatry in terms of the psychoses. As one who spent many precious years making himself respectable on psychiatric wards, in the laboratory and in organic

neurology, let me say quite explicitly that valuable though all of that may have been to me in my own emotional development, I did not begin to start to become a psychiatrist worthy of the name until I began the analytic study of the neurotic process. For this there is no substitute! Men who know all there is to know about the psychoses may still be ignorant as babes about human nature and the neuroses. From his army experiences, William C. Menninger could verify this many times over.

Furthermore, clinical maturity comes slowly to the psychiatrist. In internal medicine or surgery the house officer can see thousands of patients in a year. Not so in the study of the neuroses. Consequently, even though one learns a great deal from the intensive analytic study of a few patients which is broadly applicable to many, it takes 10 to 15 years to acquire in psychiatry the broad clinical experience that can be gained in a few years in other medical fields. I will say quite frankly that I am not proud of many things in my life; but I am proud that many years ago I had the clarity and courage to refuse several enticing academic offers which would have permanently stunted my own development by swamping me with teaching and administration and by making it impossible for me to secure analytic training and experience. And I know several other men who have had to make the same choice. In no other field of medicine do we pay as high a price as in psychiatry for burdening immature and promising young psychiatrists with academic honors which prevent their further growth.

I mention these otherwise unimportant personal experiences only because I believe that they point up a general lesson. They mean, if they mean anything, that we must re-examine our ideas of how to train psychiatrists, and of who should be trained. To this I will return later.

First, however, since everything I have to say centers around the neurosis, I would ask you to consider with me the significance of three crucial facts about the neurotic process: (1) that it is actually and in reality universal; (2) that it can and does co-exist with every other medical and surgical ill to which we are heir; and (3) that it is so often masked.

Its universality means that that preventive psychiatry of which we

have all heard so much and seen so little must somehow be made a living reality in our culture and in the medicine of the future.

Its co-existence with organic disease means that there is need for far more extensive and intensive psychiatric service in all hospitals and clinics and private offices than has ever been contemplated in the past, with far larger staffs of psychiatrists than you now conceive.

Its masking means that screening and sifting devices and personnel trained to use such devices must be made available for this work in many areas of life; not only in hospitals, but also in schools, industry, social agencies, and government.

First, then, what can we say about prevention? Over the years we have all heard much about mental hygiene and preventive psychiatry, much talk with little achievement. In the main this is because there has been no such thing as early treatment. Prevention could mean much more than treatment: but that which can be done in the nursery or in the community to prevent neuroses requires a population which is emotionally more mature, better instructed, more informed, and freer from bias and bigotry than exists. Taking the world as it is today, prevention means primarily one thing: to treat every flurry of psychiatric symptoms as a medical emergency. This means early treatment of every transitory neurotic episode of childhood. It means treatment of the adult before neuroses become fixed and irreversible. Psychiatry must cease to be always too little and too late.

Neuroses constitute the largest medical problem in the world; more universal even than a common cold in the midst of an epidemic. The so-called "neurotic" explosions of childhood are inevitable developmental episodes in the life of the normal infant and child. That which we call a psychoneurosis is merely a symptomatic crisis, a transitory or persistent period of decompensation in the course of an incessant struggle, one that goes on in every human being throughout his life, a struggle between normal and neurotic forces. The neurotic process is active in every one of us from birth to death. For the most part, it is masked, manifesting itself in our personalities, in our ways of living and working, of loving, of building families. We live not by a series of free choices but by a sequence of automatic compromises between unconscious forces and conscious forces which are engaged in a process of conflict and compromise inside of us. The neurotic epi-

sodes of infancy, childhood, and of early adolescence are the earliest crises in this conflict, moments in which the unstable dynamic equilibrium tilts in one direction or another. To handle these episodes in the traditional fashion by discipline, argument, and exhortation, by rewards and punishment, by harshness and terrorization, may drive the conflict underground but cannot resolve it. And unless the underlying conflicts are resolved, out of each such episode of psychic decompensation, the child carries a residual scar of buried tensions which limit his flexibility and his capacity to adjust to the next period of strain in his life. If, on the other hand, these early neurotic episodes are treated promptly and intensively then the conflicts can usually be resolved so completely that the individual is left with no residual difficulty, and goes on his way through life strengthened and free. This is why the use of early therapy in childhood constitutes preventive psychiatry for the adult, freeing the grownup from the crippling after-effects of the neurotic episodes of childhood. Therefore the treatment of the child and adolescent is proving to be one of the most rewarding of all experiences in medicine from the point of view of the individual; and if more widely used it can be the source of hope for a greater emotional maturity in our whole culture. Thus although the realization that neuroses are universal at first seemed dismaying, its ultimate implications offer us our best and perhaps our only hope for the future of the human race. If greed and discontent and hatred and fear are manifestations of a universal illness which can be prevented by early treatment, then we may someday conquer them; not by religion and the arts, but by science.

The next preventive step would seem to be the invasion of psychiatry into the general hospital. This, however, is worse than useless when it is as half-hearted and as under-staffed as is usual. Early treatment requires early diagnoses of incipient neurotic difficulties, diagnoses based on positive evidence and not merely on exclusion of the organic. This in turn, when applied on a large scale, means psychiatric screening. Our services learned the importance of this. The British learned it when they screened the 21st Army Group for combat before D Day. They learned it when they screened repatriated prisoners of war for return to civilian life. They learned it in the War Office Selection Board which screened candidates for officer

training school by methods not unlike those used later, and partly borrowed, by our own Office of Strategic Services.

There is evidence that psychiatric screening of initial admissions would make possible quite sizable economies in clinic and hospital practice, and ultimately in hospital re-admission rates. The percentage of unrecognized and untreated psychoneurotics among the repeaters in out-patient and hospital practice is extremely high. In hospitals therefore one of the first requirements is an adequate screening system. Such a system implies that a psychiatric appraisal should be made early in the examination of every patient, and before subjecting him to every last organic examination which could possibly throw any light on his illness. This runs counter to current practice, which tends to exhaust the possibilities of organic investigation before attempting to find out what kind of a human being the patient is.

This change in procedure would save more than time and money. The battery of organic procedures may subject patients to serious and even irreversible psychiatric damage, confirming unspoken convictions and fears that something physical must be wrong. The patient who has not been carefully prepared often feels that the doctors would not put him through so many uncomfortable, expensive, and time-consuming tests "if nothing was wrong with me." The mere fact that the results of the tests are negative means little to the patient, compared to the emotional experience of being subjected to so many examinations. The doctor comes out of the orgy of tests with the conviction that the patient is physically sound; but the patient emerges with a deep belief that he has a mysterious ailment the nature of which the doctor is hiding from him. If psychiatry becomes part of the initial screen which greets every patient when he is admitted to a general hospital, to an out-patient dispensary, or when he enters the office of the private internist or surgeon, and if all invidious distinctions are avoided by making the psychiatric examination as routine a part of the initial evaluation of every patient as is the general inspection which initiates the physical examination, or the determination of blood pressure, hemoglobin, and urinalysis,—then much of the waste motion of traditional practice could be avoided, and patients could be spared a great deal of confusion.

In practical consequences what does this mean?

For several years before the war I ran a psychiatric service in a general hospital (Kubie, 1). This was not merely a consultation service on call from ward to ward, leaving behind a trail of interesting but unused diagnoses. We set up our psychiatric service only where we were invited, and only where we were allowed to install a three-man psychiatric team as a permanent and integral part of the ward. Each psychiatric team consisted of a mature psychiatrist who had had several years of experience in the analysis of the neuroses, and under him a couple of younger analysts. Gradually as we worked along, one service after another throughout the hospital asked us to install similar units; until we had ten teams, or thirty psychiatrists, working throughout the hospital. Everywhere we had the same experience. We would begin by seeing 1 to 2 per cent of the ward population. Within six months we would be called upon to see between sixty and seventy per cent, plus many of the doctors and nurses. Indeed our colleagues used to complain at the numbers of nurses and house officers who had previously been heading towards other specialties and who now planned to become psychiatrists.

It became evident that more universally and more subtly than is realized, neurotic discontent finds a safe and happy refuge in physical illness. Just as most women are happiest in the refuge of pregnancy, so the average human being, unless he has a specific phobia of disease is actually happier when he has measles or a broken leg than when he is facing himself and the world without such an alibi. This may be true even when the illness involves great pain. Physical ailments thus serve unconscious psychological purposes identical with those of the simulated illnesses of a conversion hysteria or of other psychopathological conditions, enabling the patient to hide from emotional difficulties. So generally true is this, that we learned to be suspicious of any patient who made too comfortable an adjustment to life on the hospital ward. We learned a lesson which the army never quite accepted, namely that the model patient of the army hospital all too frequently becomes the chronic repeater of the Veterans Administration. Somewhat reluctantly therefore we faced the fact that on every ward of every hospital in every bed lies a human being who is caught in conflict between normal and neurotic life forces, a conflict from which in many instances he achieves a transitory and deceptive peace

of mind through the welcome disguise of physical illness. This in turn brings us up against the unwelcome fact that convalescence is rarely an unmixed blessing (Kubie, 2). For most men convalescence means rather a return to those lives of quiet desperation which Thoreau ascribed to all of us. Once we grasp this, it becomes our duty as physicians to bring to the surface and to treat the masked neurosis in the convalescent just as carefully as we treated his more obvious broken leg. Instead, as things go today, just as soon as the bone is set we are only too glad to dismiss our patient as "cured", returning him to his purgatory with a sigh of relief at getting him off our hands and off our wards. In the not too distant future, we may discharge our patients through convalescent pavilions where their emotional needs will receive care as expert as their broken bones.

Thus psychiatry in our hospitals can do three things: (1) It can screen at the admitting office; (2) It can treat both the patient in the hospital, and his home through the psychiatric social service of the hospital; (3) It can prepare him for the strain of a return to health. The same functions can be played by the psychiatrist in a general private practice: but only if a true partnership is created between the psychiatrist and the internist or surgeon in their private offices, identical to that which is needed in hospital organization. This partnership will have to be financial as well as scientific, if it is to meet this problem squarely.

There are many other areas of life in which psychiatry is needed, areas which do not come strictly within the province of medicine, but which complicate our problem by the demands they make on our educational facilities. Psychiatric knowledge is needed in courts, schools and colleges, in social agencies, in industry, in the introduction of young people to the problems of marriage and of child-raising (Kubie, 4). Some believe that psychiatry may even be of importance for the understanding of economic, social and governmental problems, and in dealing with the origins of inter-racial strains and international hatreds.

How many psychiatrists do we need to perform all of these tasks? If psychiatric problems confront us with significant diagnostic and therapeutic problems in 60-75 per cent of all medical practice, do we need one psychiatrist for every internist and surgeon? Fortunately

not: but it is a conservative estimate that we do need at least 30,000 men and women trained in psychiatric knowledge and technique. Where are they to come from? Kubie, (3.)

No matter how well trained he is to a psychosomatic attitude, it is not likely that the busy practitioner will ever be able to be his own psychiatrist. Even if new methods materially shorten the duration of treatment, individual psychotherapeutic sessions have to be long. Therefore, just as it is impossible for a psychiatrist or a brain surgeon to undertake general medical responsibilities, conversely, the busy doctor or surgeon cannot devote several hours out of his day to the treatment of a few patients, because to do this would interfere with too many of his other professional responsibilities. Consequently, even if the internist or surgeon could acquire the necessary psychotherapeutic techniques, the time requirements are such that he could not often serve as his own psychotherapist. Indeed experience shows that when he undertakes to do his own psychotherapy, the pressure of other professional obligations usually forces the internist or surgeon to use superficial techniques which relieve symptoms temporarily but obscure the underlying neurotic process. This, thereupon, goes on unchecked until it breaks out later in more serious form. The psychiatrist frequently sees patients to whom this has happened, especially among the patients of those internists and surgeons who are most sympathetic to psychiatry, and who therefore attempt psychotherapy on their own.

This still leaves us to face the problem of where these vast numbers of men trained in psychiatric and psychotherapeutic techniques can be recruited or trained. We know that after 1910, the drive to raise the level of medical education cut in half the number of medical schools and medical students, and that the relative number of medical students has never since caught up to the growth of the population. Nor is there any indication that our facilities for medical education will increase rapidly enough even to take care of the need for more internists and surgeons, much less to take care of this need for vast numbers of additional psychiatrists. As I have said, we need 30,000. We have 4,000; of whom 3,000 work in hospitals and only about 1,000 in community agencies and private practice. We turn out about 75 a year: barely enough to balance the annual loss from disability, old age, and

death. How can we make up this deficit? There are only four alternatives, and these are not in any sense mutually exclusive: (a) by bringing up people so free from neuroses that they will not need psychiatry; a shining goal, but hardly of immediate help; (b) by training surgeons and internists to be their own psychotherapists; as we have seen, a plan that is not likely to work well; (c) by training more psychiatrists in our regular postgraduate medical curriculum; an essential step, but one which is limited by reason of the fact that the training takes about twelve years after graduation from college; (d) finally, by training a new para-medical profession, a doctorate in medical psychology and psychotherapy.

It is sometimes argued that our medical schools and teaching hospitals should take under their wings the development of a new para-medical specialty, creating a new doctorate in medical psychology, in which men could be trained in six to seven years after a Masters degree in academic psychology, these years to include clinical apprenticeships both in general and in psychiatric hospitals. This would save about half the time which it takes to train a medical psychiatrist, thus increasing both the number of trained individuals, and the number of years each man would have in which to use his special knowledge. This would make treatment available at lower cost both to individual patients and to the community; since training which takes only five to six years can be supplied at less expense than a training which takes ten to twelve years. Clearly, the pros and cons of such a solution should be carefully considered.

On philosophic grounds, the understanding of the psychological instrument by which humans live cannot remain the exclusive field of a small band of specialists. Instead, it must become the core of our educational process; and only the specific techniques of therapy will remain the special preoccupation of the psychiatrist. The ancient Greek admonition to "Know thyself" remained an empty hope until techniques came into our possession for penetrating to the unconscious neurotic forces that determine so much of the surface of our lives. On practical grounds, if we believe that psychiatric training is important not only in medical installations but also in so many other areas of life, then clearly it will never be possible to supply all of the trained medical psychologists and psychotherapists out of the medical profession alone.

Furthermore, it might be well to keep in mind the fact that events are moving forward under the pressure of a universal human need which will not be denied. It is putting our heads in sand to pretend that we can prevent the development of some such new discipline by standing up resolutely and saying that nobody without a medical degree should ever perform any psychotherapeutic functions. Today, all over the country thousands of so-called clinical psychologists are being trained for this very purpose, but with no medical supervision or training, entirely outside of the atmosphere and tradition of therapeutic responsibility which is found in teaching hospitals and medical schools, with wholly inadequate clinical grounding, and without direct first-hand familiarity with any of the phenomena either of organic or of psychiatric illness. To shut our eyes to this is folly; and to refuse to accept responsibility for training in this field will result in the country's being flooded by people who are inadequately trained.

It is not within the scope of this paper to present a detailed analysis of what elements of the medical curriculum would be retained in the training of such a para-medical specialty, and which could be eliminated. Careful study of the curriculum indicates, however, that out of approximately 6,000 hours in the entire medical curriculum, at least one-third could be eliminated to meet the needs of a curriculum in medical psychology by devoting them to psychological and psychiatric issues. That any such plan would create difficult problems with regard to space, staffing, and financing is obvious; but the fact that the problems are difficult does not mean that they are insoluble.

The existence of a para-medical curriculum in medical psychology within the framework of our medical schools would ultimately exercise a profound reciprocal influence on medical education. The anatomy and physiology of human personality, its inter-relation with social and economic stress, and their combined influence on organic and psychiatric disease would become a part of the curriculum for medical students from their first days in school; and medical science would then become in fact the three-legged stool described so aptly by Stanley Cobb, standing firmly and equally on internal medicine, surgery and psychiatry.

There will always be a function for the medically trained psychiatrist; but the psychiatrist alone cannot be the exclusive guardian of the mental health of a whole people, in dealing with problems which

affect 130,000,000 people, and which include every aspect of their relationship to one another, and every stage in their development. Instead, those who are trained in a new para-medical psychology, widely dispersed throughout the entire life of the community, might well become a starting point for a profound cultural evolution. And at the same time within our hospitals and medical schools, through a process of healthy cross-fertilization, they might exercise a maturing influence on our medical students, and—I might add—on our medical faculties.

This whole idea has its roots in the psycho-biology which is so familiar to us here. Two levels of integration, two overlapping but not co-extensive areas of scientific knowledge, and two technical systems can best be represented not by one person but by two, two scientists who have a common goal but different aptitudes, overlapping but not identical curricula, and two coordinated systems of therapeutic methods. If, in the psycho-biological team of the future, we will train the *psycho* half as well as we have trained its *bio* half in the past; then out of the two could be formed a team which would make of psycho-biology a living reality, a reality not in medicine alone but in our whole culture.

BIBLIOGRAPHY

- (1) LAWRENCE S. KUBIE: The Organization of a Psychiatric Service for a General Hospital. *Psychosomatic Medicine*, Vol. IV, No. 3, July, 1942, pp. 252-272.
- (2) LAWRENCE S. KUBIE: Motivation and Rehabilitation. *Psychiatry*, Vol. 8, No. 1, 69-78, Feb. 1945.
- (3) LAWRENCE S. KUBIE: A Program of Training in Psychiatry to Break the Bottleneck in Rehabilitation. *Amer. Jour. of Orthopsychiatry*. Vol. XVI, No. 3, July 1946.
- (4) LAWRENCE S. KUBIE: Psychiatry and the Films. *Hollywood Quarterly*, Volume 2, No. 2, January 1947.
- (5) LAWRENCE S. KUBIE: Medical Responsibility for Training in Clinical Psychology. (In press.)

BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers
and not necessarily those of the members of the Editorial
Board of this Journal)

The Anatomy of the Nervous System. By STEPHEN W. RANSON AND SAM L. CLARK.
8th Ed. Illus. 532 pp. \$6.50. *W. B. Saunders Company, Philadelphia,
Pennsylvania, 1947.*

This is the latest revision of Ranson's widely used text, and the first under the editorship of Professor Clark. The book is slightly larger—12 pages and 9 figures have been added—than the 1943 edition, and the general style of presentation is unchanged. Certain chapters and parts of chapters have been reshuffled to increase the integration and continuity of the text. For example, the gross anatomical descriptions, which previously were scattered throughout the book, are here grouped into one chapter. Numerous additions from the experimental literature are found, and the discussion of clinical cases has been partly rewritten and improved. The discussion of cortical localization has received much needed attention, but the significant, recent contributions to sensory localization are still sadly neglected. The reviewer's special interest in the histogenesis of nervous tissue, and in the motor system of the spinal cord is unsatisfied by this part of the book, because of the editor's neglect of many important contributions. The recent histochemical studies of chromatolysis are not mentioned here. Many of the papers cited in the text have not been added to the bibliography.

The new editor should be complimented on the improvement of this volume over its already excellent predecessor, and it is to be hoped that the few still patent weaknesses will be corrected in future editions.

J. M. S.

The Compleat Pediatrician. By W. C. DAVISON. 4th Ed. 256 pp. \$3.75.
Duke University Press, Durham, North Carolina, 1946.

This is the fourth edition of Dr. Davison's book. The preface emphasizes the fact that the volume is "an effort to compile and record briefly those practical pediatric facts, which though essential, usually slip from memory." The *Compleat Pediatrician* does contain an amazing amount of useful information, clearly stated and readily available. There are sections which list the diseases involving the various systems of the body, briefly enumerating the important signs and symptoms of each. However, the sections on laboratory procedures, general treatment and nursing, drugs and prescriptions appear to be of most practical value and cover material which is usually lacking in standard pediatric text books. Such techniques as cisternal puncture, parenteral administration of fluids, skin testing, etc., are rather fully described and make the book most useful to the interne in pediatrics

or to the practitioner who is required to carry out these procedures. In the section on laboratory methods are listed tests in common use in the study of diseases of children, given in sufficient detail to warrant its use as a laboratory manual. The practicality of this little book may be illustrated by the fact that it even includes a section listing essential drugs and equipment for a pediatrician's bag. The title page of the *Compleat Pediatrician* states that it is written for the use of medical students, internes, general practitioners and pediatricians. The book appears to be of little value as far as medical students are concerned. It is far too practical for their purposes and by its very nature cannot elaborate on the fundamentals necessary for basic training in pediatrics. As a reference book, the *Compleat Pediatrician* does have its place in the library of the interne, general practitioner, and pediatrician.

S. G.

Chronic Disease and Psychological Invalidism, a Psychosomatic Study. By JURGEN RUESCH. 191 pp. \$3.00. *The American Society for Research in Psychosomatic Problems, New York, New York, 1946.*

The authors have investigated the economic, social, physical and psychological factors which influence the course of chronic disease and psychological invalidism. Psychoneurotic patients without physical symptoms were excluded and the symptoms had to persist over a period which exceeded the time commonly needed for recovery.

There were 187 cases ranging in age from 13 to 73 years with a mean age of 35.3 years. In 91% of the cases of delayed recovery there was reported 1: pain in a variety of locations. 2: gastrointestinal symptoms. 3: anxiety features.

Two groups of cases are differentiated. A: those who had a diagnosed or identified disease. B: those who never did. The former group is comprised of individuals who have "physical disease with psychological complications" while the latter group consisted primarily of "psychoneuroses with physical complications."

In 73% of the patients there were self-destructive tendencies found as being significant for their delayed recovery. Only 15% of the patients experienced impersonal or external change in their life situations as compared with 45% of the patients who were exposed to significant alterations in their intimate, human environment.

There is included an account of the pertinent psychological problems in general medicine.

This monograph can be highly recommended to every student of medicine. The surgeon, who is confronted with patients who are overly-anxious to be operated upon, or who already have had multiple operative procedures, the orthopedist, who is faced with a patient who is accident prone and who has had a history of more than the expected number of fractures, the physician, who is puzzled by the patient who has a tendency to be "susceptible" to multiple illnesses, will be better able to understand the motivations and character structure of their patients after reading this book.

J. H. C.

Differential Diagnosis of Jaundice. By LEON SCHIFF. Illus. 313 pp. \$10.00. The Year Book Publishers, Chicago, Illinois, 1946.

Dr. Schiff has organized a very excellent gastroenterological department at the University of Cincinnati and Cincinnati General Hospital. This monograph has the authority of that department as well as of Dr. Schiff's excellent personal reputation. The subject of jaundice is always a complicated one. There are few physical signs in medicine and surgery that are so protean in their causation and mechanism as is jaundice.

The book considers the classification of jaundice, and then considers separately, parenchymal jaundice, neoplastic jaundice, calculous jaundice, retention jaundice, and a separate section on jaundice of the neonatal period. Finally, there are sections on the clinical and laboratory diagnosis of jaundice. The newer tests, such as thymol turbidity received adequate notice.

The work of Rich and of McNee is given due credit, and the book is furnished with an adequate and extremely up-to-date bibliography. It can be safely recommended as profitable reading to all practitioners and students.

H. H.

Diseases of the Retina. By HERMAN ELWYN. Illus. 587 pp. \$10.00. The Blakiston Company, Philadelphia, Pennsylvania, 1946.

This volume is divided into eight sections dealing with disturbances in circulation, vascular malformations, hereditary changes, inflammatory diseases, tumors, conditions leading to retinal detachment, developmental anomalies and injuries of the retina from radiant energy.

The volume is well written, the subject matter is comprehensive, there are well constructed descriptions of many disease entities which, heretofore, have either been ignored or inadequately described in the conventional text-books on ophthalmology. The book is, therefore, thoroughly worth while and merits a place in every ophthalmological library.

There are, however, definite weaknesses in some of the presentations. First, there is too often a tendency to consider the retina as a separate structure especially vulnerable to certain morbid processes, rather than as an integral part of a complex organ subject to the general pathologic processes, infection and resistance, which affect the body as a whole. Thus the chapters on syphilis and tuberculosis of the retina appear quite inadequate. A similar criticism may be registered against the chapters on vascular diseases. For example, serious exception might be taken to the definition that "arteriosclerosis or hardening of the arteries is one and the same disease whether the intima presents an ulcer containing mush, an 'atheroma', a localized fibrous thickening, or a hyaline thickening of the arterioles", and to the subsequent discussion based on this premise. Second, on contraversial subjects as a rule only one side of the question is presented, and, while there is a bibliography at the end of each section, this is usually incomplete and gives only the literature utilized in this presentation, or which coincides with the author's opinion.

Despite these criticisms, which in essence are really only a reflection of the

author's individual views, this book brings together in one concise volume a mass of material and wealth of information, much of which has been pretty well buried in the literature. Despite its shortcomings, it is a commendable piece of work and is to be recommended to ophthalmologists.

A. C. W.

Early Ambulation And Related Procedures In Surgical Management. By DANIEL J. LEITHAUSER. 232 pp. \$4.50. Charles C Thomas, Springfield, Illinois, 1946.

This volume dealing with a currently controversial and live subject is written by an author who has been one of the leading and most uncompromising proponents of his subject, and one to whom much credit must go for the spread of the "gospel" he preaches. Claiming no originality for this theory, he propounds in logical sequence the reasons why "early rising" prevents complications and hastens convalescence. He insists upon his definition as meaning "immediate" (i.e. day-of-operation) rising and decries the attitude of his compromising colleagues who follow an attitude of "wait and see" or "happy medium". Ambulation includes not only standing and walking, but coughing in the upright position with the clearing of mucus and disappearance of rales. Chapter by chapter he tersely and convincingly reviews the ordinary groups of complications, and, supported by an experience of 2047 patients shows the beneficial effect of his program. Finally, he puts forth a plan of surgical management based upon his own experience which he considers essential before early ambulation may be permitted. This includes details of pre-operative care, anaesthesia, surgical technic including suture material, postoperative care, and finally, the details of early rising itself. This is a brief treatise, well documented with modern references to support the thesis, a convincing treatise which every doubting surgeon should read so that he may better understand the problem which is being attacked and the position of a practical surgeon who speaks with authority about a radical departure in surgical practice.

S. McL.

Harvey Cushing. By JOHN F. FULTON. Illus. 754 pp. \$5.00. Charles C Thomas, Springfield, Illinois, 1946.

This is the story of one of the great men in medicine. If it is read, not word by word, but with understanding, the medical student will get an inspiration that will greatly aid him to rise above mediocrity and climb to the top of the ladder in his chosen profession. The secrets of success, as exemplified in the life of Harvey Cushing, are a strong healthy body (he was an exceptionally good athlete in the gymnasium, on the baseball field and at tennis), a charming personality that won for him friends in all parts of the world, and a broad basic education. From his youth he was a perfectionist, and throughout his life he took infinite pains to make his addresses, his publications and his care of patients as near perfect as it was possible to make them. He was a firm believer in the value of clinical research,

supplemented, where additional knowledge could be gained, by animal experiments. His pioneer work on the functions and diseases of the pituitary gland is a striking example of his brilliant mind.

Added to these characteristics was the stimulus he received from years of close association with Halsted, Osler, Welch, Simon Flexner, Mall, Councilman and others during the early years of the Johns Hopkins Medical school and hospital. From these men he acquired the curiosity to find out why, and the ambition to be a contributor, rather than a parasite living and practicing on the fruits of the labors of others.

The ambition thus acquired never left him, but grew year by year. Osler interested him in the history of medicine. This led to the remarkable collection of books and manuscripts, which he left to Yale University. He not only collected these books, but educated himself to read them in the original. He was an inspiring and fascinating teacher. On ward rounds he invariably showed students books illustrating the growth of knowledge throughout the centuries concerning the malady of the patient under discussion.

He was impatient of carelessness and lack of consideration for the patient. He emphasized, often with stinging rebukes to his house officers, that no effort must be spared to give the sick patient the best that is in you, regardless of race, color, creed or financial status.

I know of no medical biography that can be read with greater benefit to the student than John Fulton's life of Harvey Cushing.

S. J. C.

Introduction to Surgery. By VIRGINIA KREELAND FRANTZ, AND HAROLD DORTCH HARVEY. 216 pp. \$2.50. *Oxford University Press, New York, New York,*

This stimulating and provocative monograph is an outgrowth of the introductory course in surgery given to medical students in their second year at the College of Physicians and Surgeons of Columbia University. Most of the text is concerned with the reparative process of the tissues in response to injury and/or infection. The reviewer is heartily in accord with the authors in their desire to create in the student an inquiring and critical mind, unhampered by the acceptance of dogma. Nearly every paragraph in the monograph provides, in the words of the authors, "food for thought and basis for argument". Students and young surgeons will profit from a thoughtful reading of this excellent little book.

E. S. S.

Chemotherapy, Yesterday, Today, and Tomorrow. By SIR ALEXANDER FLEMING. 39 pp. \$.50. *The Macmillan Company, New York, New York, 1947.*

In his Linacre Lecture, Alexander Fleming has simply and effectively told the story of chemotherapy as it has unfolded during the past century. This lecture is factual, coherent and interesting. It makes excellent reading for both the physician and the layman.

P. H. L.

Medical Biochemistry. By MARK R. EVERETT. 2nd Ed. 767 pp. \$7.00.
Paul B. Hoeber, Incorporated, New York, New York, 1946.

For the first edition of this work, the author expressed the ambition to make it "a text in consonance with modern teaching, which includes the essential facts and fundamental data, . . . and is of such a size that the student will have time to read it." The plan seems to have been abandoned in this, the second, edition which sets out to accomplish two rather irreconcilable objectives. The book seems now intended to serve both as a convenient reference volume and as a text for various types of medical biochemistry courses, including the basic course.

The ten chapters deal with: acid-base relations; colloids, enzymes, and oxidation; digestion; lipids; carbohydrates; proteins; prosthetic radicals of proteins; inorganic substances; vitamins and avitaminoses; and, hormones and endocrines. In most cases, each chapter is subdivided under the headings, chemistry, metabolism, and pathology, and closes with a selection of representative general references. The text and the numerous tables present a great mass of information, the reliability of which, in the absence of specific references, is not always easy to assess. For example, only the more experienced student would be suspicious of the curious information that oxyhemoglobin has a pK of 6.62 and hemoglobin a pK of 8.18.

The exposition of subject matter is generally didactic, and often exceedingly brief. One finds little of the lucid and cogent exposition needed in the elementary training of students in medicine. The treatment of acid-base relations is somewhat archaic. The subject of digestion is properly allocated to a separate chapter, whereas the equally, if not more, important subject of the respiratory functions of the blood is scattered as parts of several different chapters. This scattering is perhaps justifiable from a narrow standpoint of "systematization", but it hardly meets the need of the medical student for an integrated concept of one of the more significant aspects of medical biochemistry.

Many of the numerous tables contain interesting and important data in condensed form, some of which the teacher or investigator may find useful.

B. C.

Muscle Testing. Techniques of Manual Examination. By LUCILLE DANIELS, MARIAN WILLIAMS AND CATHERINE WORTHINGHAM. Illus. 189 pp. \$2.50.
W. B. Saunders Company, Philadelphia, Pennsylvania, 1946.

Manual muscle testing is an important division of Physical Therapy and is studied both qualitatively and quantitatively. This volume presents muscle topography, muscle function, joint range, and nerve distribution and utilizes 349 diagrammatic line drawings. The physical therapist will appreciate the clear, succinct instructions and the admirable, simple illustrations.

This useful work will be welcomed by physical therapists, by orthopedists, and by other students of the skeletal structure.

T. P. S.

New Aspects of John and William Hunter. By JANE M. OPPENHEIMER. 188 pp. \$6.00. Henry Schuman, New York, New York, 1946.

This book, in a limited edition, is well printed, well illustrated, well annotated, and more important, very well written. It is a worthy addition to the already extensive literature about the earlier of the two most famous pairs of medical brothers. In the present volume, the first part considers an investigation of the facts leading up to Sir Everard Home's destruction of the John Hunter Manuscripts. With well supported logic, Dr. Oppenheimer convicts Home of burning these manuscripts to cover his own extensive plagiarisms. Since the burning occurred thirty years after Hunter's death, there was ample time to cull the manuscripts for their best, which may have been the basis of Home's own over one hundred publications.

The second part discusses William Hunter's relationship with his lay contemporaries, a subject previously much neglected.

This reviewer's only criticism of this excellent book is that the annotations are placed, undoubtedly for the sake of appearance, at the end of each section. Since they are all of great interest to careful readers, their correlation with the text involves a deal of page turning. This book should be of interest to all medical historians and particularly to all those who have puzzled about various unsolved mysteries in the lives of the two Hunter brothers.

H. N. H.

Outline of the Spinal Nerves. By JOHN FAVILL. Illus. 191 pp. \$3.75. Charles C Thomas, Springfield, Illinois, 1946.

This little book will undoubtedly prove to be very useful to neurologists and to neurosurgeons. The author has collected all the information about the anatomy, composition and function of the spinal nerves as well as the skeletal muscles. All of the standard text books have been analysed and compared. Where these authorities differ, the author has made his own choice. These facts are presented very briefly but in such a systematic fashion that it is easy to find the information desired.

F. R. F.

Uterine Contractility in Pregnancy. By DOUGLAS P. MURPHY. Illus. 134 pp. \$5.00. J. B. Lippincott Company, Philadelphia, Pennsylvania, 1947.

This small volume of 134 pages covers observations with the Lorand tocograph on the uterine activity of 1153 individuals during both pregnancy and labor. Many of the records and observations have been previously published in various scientific journals.

The format is excellent. The book is divided into six sections of several chapters each. These divisions are logical for a study of this type and include a discussion of material and methods and a general summary. In addition there are observations on spontaneous uterine activity and factors influencing this activity,

during pregnancy and labor. There are two major criticisms of this work. The first is a lack of thoroughness of discussion regarding the tocograph itself. No real investigation appears to have been made to determine the degree of variation inherent in the instrument itself, or the effect of its positioning or methods of attachment to the abdomen. Using more sensitive devices all of these factors appear to play an important role and there is no reason to suppose that the tocograph is immune to this variability. Nor is the discussion of what is measured by this instrument convincing. Apparently the author accepts without reservation the work of Wolfe that the degree of uterine hardness is what is recorded.

The second major criticism is based on the conclusions drawn. So long as observations are presented these make contributions to our knowledge and are of great interest. The division of pregnancy into three phases of uterine activity, the study of types of uterine inertia as related to tocograph charts, the effects of morphine, estrogen and pituitrin on these graphs are all valuable and important contributions. There is no proof, however, that the statement that the early appearance of uterine activity is related to the duration of pregnancy is valid. As regards the use of the statistical method to prove that early contractions influence the duration of labor, the samples are so small as to make such an approach not only unjustified but meaningless. For example, the duration of labor in primigravidae with early contractability is based on but three cases. Similarly, the character of the uterine response to pituitrin and its relation to the duration of labor is submitted to statistical attack which is invalid on the same basis.

The importance of this volume is in its emphasis on our lack of knowledge of uterine physiology during normal and abnormal labors. While many of its conclusions are not proven certain observations are of importance. With more sensitive and accurate instruments and a study of a great many more cases, and with this small volume as a guide post those phases of uterine activity about which we today know so little, should become clear.

L. M. H.

BOOKS RECEIVED FOR REVIEW

- Anesthesia in General Practice.* By STUART C. CULLEN. Illus. 260 pp. \$3.50. The Year Book Publishers, Chicago, Illinois, 1946.
- Allergy in Theory and Practice.* By ROBERT A. COOKE. Illus. 572 pp. \$8.00. W. B. Saunders, Philadelphia, Pennsylvania, 1947.
- The Anatomy of the Bronchial Tree.* By R. C. BROCK. Illus. 96 pp. \$12.00. Oxford University Press, New York, New Ycrk, 1946.
- The Anatomy of the Nervous System.* By STEPHEN WALTER RANSON. 8th Ed. Illus. 532 pp. \$6.50. W. B. Saunders, Philadelphia, Pennsylvania, 1947.
- An Integrated Practice of Medicine.* By HAROLD THOMAS HYMAN. Vols. 1-4 and Index. Illus. 4131 pp. \$50.00. W. B. Saunders Company, Philadelphia, Pennsylvania, 1946.
- Cardiovascular Diseases.* By DAVID SCHERF and LINN J. BOYD. Illus. 478 pp. \$10.00. J. B. Lippincott Company, Philadelphia, Pennsylvania, 1947.
- The Centennial of Surgical Anesthesia.* Compiled by JOHN F. FULTON and MADELINE E. STANTON. 102 pp. \$4.00. Henry Schuman, New York, New York, 1946.
- The Challenge of Polio.* By ROLAND H. BERG. 208 pp. \$2.50. The Dial Press, New York, New York, 1946.
- Chemotherapy—Yesterday, Today and Tomorrow.* By SIR ALEXANDER FLEMING. 39 pp. \$50. The Macmillan Company, New York, New York, 1947.
- Chronic Disease and Psychological Invalidism, a Psychosomatic Study.* By JURGEN RUESCH. 191 pp. \$3.00. The American Society for Research in Psychosomatic Problems, New York, New York, 1946.
- Clinical Hematology.* By MAXWELL M. WINTROBE. 2nd Ed. Illus. 862 pp. \$11.00. Lea and Febiger, Philadelphia, Pennsylvania, 1946.
- The Compleat Pediatrician.* By W. C. DAVISON. 5th Ed. 256 pp. \$3.75. Duke University Press, Durham, North Carolina, 1946.
- The Diagnosis and Treatment of Bronchial Asthma.* By LESLIE N. GAY. 334 pp. \$5.00. The Williams & Wilkins Company, Baltimore, Maryland, 1946.
- Differential Diagnosis of Jaundice.* By LEON SCHIFF. Illus. 313 pp. \$10.00. The Year Book Publishers, Chicago, Illinois, 1946.
- Diseases of the Retina.* By HERMAN ELWYN. Illus. 587 pp. \$10.00. The Blakiston Company, Philadelphia, Pennsylvania, 1946.
- Disorders of the Blood.* By LIONEL E. H. WHITBY and C. J. C. BRITTON. 5th Ed. Illus. 665 pp. \$10.00. The Blakiston Company, Philadelphia, Pennsylvania, 1946.
- Edinburgh Post-Graduate Lectures in Medicine.* Vol. III. Published for the Honyman Gillespie Trust. 587 pp. \$15.00. Oliver and Boyd, Tweeddale Court, Edinburgh, 1946.
- The Eye Manifestations of Internal Diseases.* By I. S. TASSMAN. 2nd Ed. Illus. 614 pp. \$10.00. The C. V. Mosby Company, Saint Louis, Missouri, 1946.

- Gynecological and Obstetrical Pathology.* By EMIL NOVAK. 2nd Ed. Illus. \$7.50. W. B. Saunders Company, Philadelphia, Pennsylvania, 1947.
- Harvey Cushing.* By JOHN F. FULTON. Illus. 754 pp. \$5.00. Charles C Thomas, Springfield, Illinois, 1946.
- Henry Sewall.* By GERALD B. WEBB and DESMOND POWELL. Illus. 191 pp. \$7.50. The Johns Hopkins Press, Baltimore, Maryland, 1946.
- Heparin in the Treatment of Thrombosis.* By J. ERIK JORPES. 2nd Ed. Illus. 260 pp. \$6.50. Oxford University Press, New York, New York, 1947.
- Hippocratic Wisdom.* By WILLIAM F. PETERSEN. Illus. 263 pp. \$5.00. Charles C Thomas, Springfield, Illinois, 1946.
- Introduction to Surgery.* By VIRGINIA KNEELAND FRANTZ and HAROLD DORTCH HARVEY. 216 pp. \$2.50. Oxford University Press, New York, New York, 1946.
- A Memoir to the Academy of Science at Paris on a New Use of Sulphuric Ether: 1847.* By W. T. G. MORTON. 24 pp. \$1.50. Henry Schuman, New York, New York, 1946.
- Muscle Testing. Techniques of Manual Examination.* By LUCILLE DANIELS, MARIAN WILLIAMS and CATHERINE WORTHINGHAM. Illus. 189 pp. \$2.50. W. B. Saunders Company, Philadelphia, Pennsylvania, 1946.
- The Nervous Child.* By HECTOR CHARLES CAMERON. 5th Ed. Illus. 252 pp. \$3.00. Oxford University Press, New York, New York, 1946.
- Nursing Care in Chronic Diseases.* By EDITH L. MARSH. Illus. 237 pp. \$3.00. J. B. Lippincott Company, Philadelphia, Pennsylvania, 1946.
- Office Endocrinology.* By ROBERT B. GREENBLATT. 3rd Ed. Illus. 303 pp. \$4.75. Charles C Thomas, Springfield, Illinois, 1947.
- Operative Gynecology.* By RICHARD W. TE LINDE. Illus. 751 pp. \$18.00. J. B. Lippincott Company, Philadelphia, Pennsylvania, 1946.
- Outline of the Spinal Nerves.* By JOHN FAVILL. Illus. 191 pp. \$3.75. Charles C Thomas, Springfield, Illinois, 1946.
- Parenteral Alimentation in Surgery.* By ROBERT ELMAN. 284 pp. \$4.50. Paul B. Hoeber, Inc., New York, New York, 1947.
- Pharmacology and Therapeutics.* By ARTHUR GROLLMAN and DONALD SLAUGHTER. 13th Ed. Illus. 868 pp. \$8.50. Lea & Febiger, Philadelphia, Pennsylvania, 1947.
- Philosophy and Medicine in Ancient Greece.* By W. H. S. JONES. 100 pp. \$2.00. The Johns Hopkins Press, Baltimore, Maryland, 1946.
- Quantitative Clinical Chemistry Interpretations.* By JOHN P. PETERS and DONALD D. VAN SLYKE. Vol. 1. 2nd Ed. 1041 pp. \$7.00. The William & Wilkins Company, Baltimore, Maryland, 1946.
- Sexual Inadequacy of the Male.* By PAUL POPENOE. 41 pp. \$1.00. The American Institute of Family Relations, Los Angeles, California, 1947.
- Sex Education.* By CRIL BIBBY. 311 pp. \$2.50. Emerson Books, Incorporated, New York, New York, 1946.

- The Story of Human Birth.* By ALAN F. GUTTMACHER. 214 pp. \$.25. *Penguin Books, Incorporated, New York, New York, 1947.*
- Surgical Treatment of the Soft Tissues.* By FREDERIC W. BANCROFT and GEORGE H. HUMPHREYS. Illus. 520 pp. \$15.00. *J. B. Lippincott Company, Philadelphia, Pennsylvania, 1946.*
- Textbook of Clinical Neurology.* By J. M. NIELSEN. 2nd Ed. Illus. 699 pp. \$7.50. *Paul B. Hoeber, Incorporated, New York, New York, 1946.*
- The Thyroid Gland in Medical History.* By ALFRED H. LASON. 136 pp. \$3.00. *Froben Press, New York, New York, 1946.*
- Urgent Surgery.* Edited by JULIUS L. SPIVACK. Vol. 1. Illus. 714 pp. \$10.00. *Charles C Thomas, Springfield, Illinois, 1946.*
- Uterine Contractility in Pregnancy.* By DOUGLAS P. MURPHY. Illus. 134 pp. \$5.00. *J. B. Lippincott Company, Philadelphia, Pennsylvania, 1947.*
- Victory over Pain.* By VICTOR ROBINSON. 338 pp. \$3.50. *Henry Schuman, New York, New York, 1946.*

INDEX TO VOLUME LXXX

Pagination according to months:

January, 1-106

February, 107-148

March, 149-180

April, 181-216

May, 217-298

June, 299-375

Albanese, Anthony A: Studies on the Protein Metabolism of the Infant. I. The Comparative Biological Value of Some Milk Protein Preparations	149
Antipellagra Action of N ¹ -Methylnicotinamide. Najjar, Victor A. and Deal, Carolyn C.	166
Backache	217
Bing, R. J: Physiological Studies in Congenital Heart Disease. I. Procedures.....	107
Bing, R. J: Physiological Studies in Congenital Heart Disease. II. Results of Pre-operative Studies in Patients with Tetralogy of Fallot	121
Bing, R. J: Physiological Studies in Congenital Heart Disease. III. Results Obtained in Five Cases of Eisenmenger's Complex.	323
Book Reviews.....	174, 206, 361, 369
Burch, G. E: Objective Studies of Some Physiologic Responses in Mild Chronic Trench Foot	1
Cerebellopontile Angle, Tumors of	254
Cockerill, Eleanor E: Use of the Psychosomatic Concept in Social Case Work	86
Curare, Vascular Effects	299
Deal, Carolyn C. (See Najjar, Victor A.)	166
Deutsch, Felix: Use of the Psychosomatic Concept in Medicine	71
Disappearance Time of Treponema Pallidum from Lesions of Early Syphilis Following Administration of Crystalline Penicillin G. Tucker, Harold A. and Robinson, Raymond C. V.	169
Elimination of Poliomyelitis Virus from the Human Mouth or Nose. Ward, Robert and Walters, Burrill	98
Foot, Trench, Physiologic Responses	1
Gray, F. D., Jr. (See Bing, R. J.)	107, 121, 323
Gantt, W. Horsley (See Robinson, Janice)	231
Grob, D: On Certain Vascular Effects of Curare in Man: The Histamine Reaction.....	299
Harkins, Henry N: Prevention of Pyloric Ligation-Induced Ulcers of the Gastric Rumen of Rats by Transabdominal Vagotomy: A Preliminary Report	174
Harvey, A. M. (See Grob, D.)	299

Heart, Congenital Abnormality: Physiological Studies.....	107, 121, 323
Holt, L. Emmett, Jr. (See Albanese, Anthony A.).....	149, 158
Histamine-Like Effects of Curare.....	299
Idiopathic Low Back Pain and Sciatica—25 Years Ago and Now. Key, J. Albert.....	217
Impact of Modern Psychiatry on Medical Education, Medical Practice and Hospital Organization. Kubie, Lawrence, S.....	348
Irby, Virginia (See Albanese, Anthony A.).....	149, 158
Johns Hopkins Medical Society, Proceedings of Meetings.....	202, 297
Key, J. Albert: Idiopathic Low Back Pain and Sciatica—25 Years Ago and Now.....	217
Kubie, Lawrence S: Impact of Modern Psychiatry on Medical Education, Medical Practice and Hospital Organization.....	348
Latta, Harrison: Pulmonary Edema and Pleural Effusion Produced by Acute Alpha-Naphthyl Thiourea Poisoning in Rats and Dogs.....	181
Lein, Marilyn (See Albanese, Anthony A.).....	149, 158
Lilienthal, J. L., Jr. (See Grob, D.).....	299
Lipotropic Effect of N ¹ -Methylnicotinamide. Najjar, Victor A. and Ratchiffe, Idalina M.....	142
Lungs, Edema of, Produced by Acute Alpha-Naphthyl Thiourea Poisoning in Rats and Dogs.....	181
Micrococcus Tetrigenus, Cause of Penile Ulcer.....	198
Myers, Harvey L. (See Burch, G. E.).....	1
Najjar, Victor A: Antipellagra Action of N ¹ -Methylnicotinamide.....	166
Najjar, Victor A: Lipotropic Effect of N ¹ -Methylnicotinamide.....	142
Nerves, Vagus, Effect of Transabdominal Section on Gastric Ulcer Formation.....	174
Neurinomas of the Cerebellopontile Recess—A Clinical Study of One-Hundred and Sixty Cases Including Operative Mortality and End Results. Revilla, Antonia, Gonzalez.....	254
Nicotinic acid, N ¹ -Methyl-amide, Anti-pellagra Action.....	166
Nicotinic acid, N ¹ -Methyl-amide, Lipotropic Effect.....	142
Objective Studies of Some Physiologic Responses in Mild Chronic Trench Foot. Burch, G. E., Myers, Harvey L., Porter, Reno R. and Schaffier, Nathan.....	1
On Certain Vascular Effects of Curare in Man: The Histamine Reaction. Grob, D., Lilienthal, J. L., Jr., and A. M. Harvey.....	299
Orienting Reflex (Questioning Reaction): Cardiac, Respiratory, Salivary and Motor Components. Robinson, Janice and Gantt, W. Horsley.....	231
Penicillin G, Effect on Spirocheta Pallida.....	169
Prevention of Pyloric Ligation-Induced Ulcers of the Gastric Rumen of Rats by Transabdominal Vagotomy: A Preliminary Report. Harkins, Henry N.....	174
Penile Ulcer Caused by Micrococcus Tetrigenus. Pinck, Bernard D. and Zheutlin, Bertram.....	193

Peptic Ulcer, Effect of Vagotomy on Experimental Production	174
Physiological Studies	107, 121
Physiological Studies in Congenital Heart Disease. I. Procedures. Bing, R. J., Vandam, L. D. and Gray, F. D., Jr.	107
Physiological Studies in Congenital Heart Disease. II. Results of Preoperative Studies in Patients with Tetralogy of Fallot. Bing, R. J., Vandam, L. D. and Gray, F. D., Jr.	121
Physiological Studies in Congenital Heart Disease. III. Results Obtained in Five Cases of Eisenmenger's Complex. Bing, R. J., Vandam, R. J. and Gray, F. D., Jr.	323
Pinck, Bernard D: Penile Ulcer Caused by Micrococcus Tetragenus.	198
Pleural Effusion Produced by Acute Alpha-Naphthyl Thiourea Poisoning in Rats and Dogs.	181
Poliomyelitis Virus in Mouth and Nose	98
Porter, Reno R. (See Burch, G. E.)	1
Protein in Diet, Biological Value of Preparation of Milk Proteins.	149
Pshchiatry, Influence on Medicine and Hospital.	348
Psychiatry, Use in Medicine.	71
Psychiatry, Use in Social Case Work.	86
Pulmonary Edema and Pleural Effusion Produced by Acute Alpha-Naphthyl Thiourea Poisoning in Rats and Dogs. Latta, Harrison.	181
Ratcliffe, Idalina M. (See Najjar, Victor A.)	142
Reflex, Orienting	231
Revilla, Antonio Gonzalez: Neurinomas of the Cerebellopontile Recess—A Clinical Study of One-Hundred and Sixty Cases Including Operative Mortality and End Results.	254
Robinson, Janice: Orienting Reflex (Questioning Reaction): Cardiac, Respiratory, Salivary and Motor Components.	231
Robinson, Raymond C. V: (See Tucker, Harold A.)	169
Schaffer, Nathan (See Burch, G. E.)	1
Sciatica	217
Snyderman, Selma E. (See Albanese, Anthony A.)	149, 158
Spirocheta Pallida, Disappearance Time after Penicillin G Administration.	169
Studies on the Protein Metabolism of the Infant. I. The Comparative Biological Value of Some Milk Protein Preparations. Albanese, Anthony A., Holt, L. Emmett, Jr., Irby, Virginia, Snyderman, Selma E. and Lein, Marilyn.	149
Studies on the Protein Metabolism of Infants. II. Tryptophane Requirement of the Infant. Albanese, Anthony A., Holt, L. Emmett, Jr., Irby, Virginia, Snyderman, Selma E. and Lein, Marilyn.	158
Syphilis, Treatment with Penicillin	169
Thiourea, Alpha Naphthyl, Poisoning.	181
Tryptophane Requirements of Infant.	158
Tucker, Harold, A: Disappearance Time of Treponema Pallidum from Lesions of Early Syphilis Following Administration of Crystalline Penicillin G.	169

INDEX TO VOLUME LXXX

375

Use of the Psychosomatic Concept in Medicine. Deutsch, Felix.....	71
Use of the Psychosomatic Concept in Social Case Work. Cockerill, Eleanor E.....	86
Vandam, L. D. (See Bing, R. J).....	107, 121, 323
Ward, Robert: Elimination of Poliomyelitis Virus from the Human Mouth or Nose. . .	93
Zheutlin, Bertram (See Pinck, Bernard D.).....	198